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STUDIES ON THE LESIONS INDUCED BY THE ACTION OF CERTAIN POISONS ON THE CORTICAL NERVE CELL.

STUDY VII.

POISONING WITH PREPARATIONS OF THE THYROID GLAND.

By Henry J. Berkley, M. D., *Associate in Neuro-Pathology, The Johns Hopkins University.*

The favorable side of the administration of the thyroid extracts is shown in the very numerous articles in current medical literature published both in this country and in Europe. Comparatively few of these papers treat of other than the bare clinical results from the most auspicious standpoint, and it is quite safe to say, after a review of some of them, that the results would have been as brilliant had no medicament been administered.

It is nevertheless true that the extract, when administered to either man or the lower animals, will occasion very grave symptoms of a toxæmic nature, symptoms that involve the cerebral, the vaso-motor and digestive functions, and perhaps also the normal action of those ductless glands that throw into the circulation a potent though unknown substance; and when this administration is pushed even to a moderate degree death is almost invariably the result, either through the advent of convulsions, or extensive loss of weight with indications of profound poisoning of the central nervous system, shown by the change in the heart's action and in the respiratory movements.

A medicament having these qualities cannot, therefore, be administered with impunity to every sane or insane patient, and it was therefore directly for the purpose of ascertaining the toxicity of one of the best known varieties of the thyroid extract that the following series of experiments was undertaken.

The first portion of the investigation was made upon eight patients at the City Asylum, who, with one exception (No. 1), had either passed or were about to pass the limit of time in which recovery could be confidently expected. To these patients the thyroid tablets, each pill representing five grains of the fresh sheep's gland, were administered, the dosage beginning always with a single pill daily for a period of three days, then, after a certain tolerance had been established the dosage was increased to two tablets daily, and, unless the symptoms induced became grave, the number of pills was increased to three daily, the length of continuance depending upon the results.

Loss of weight always attended the administration of the tablets, as did disturbances of the circulation in the form of tachycardia and enfeeblement of the cardiac action. Digestive disturbances and slight pyrexia were present in more than half the cases. A peculiar odorous sweating was noticed with two patients, and increase of the cutaneous transpiration in

all. Irritability and a greater or less degree of mental and motor excitement were remarked in all cases, no matter how depressed or demented they had been previous to the administrations. Two patients became frenzied, and of these one died before the excitement had subsided, the immediate cause of the exitus being an acute disseminated tuberculosis. A peculiar gelatinous feel to the integument of the forehead and cheeks, precisely similar to that in myxœdema, combined with puffiness of the skin about the malar prominences, was very noticeable in those cases in which the administration of the extract was continued for any length of time. Urinary examinations were made several times before the commencement of the administration of the thyroid, and several times during its administration, but only for the purpose of noting the presence or absence of albumen and sugar. In the abstracts this analysis is mentioned only when there is evidence of the presence of these abnormal constituents.

Abstracts of Histories of Insane Patients Treated with Thyroid Extract.

I. *Adolescent insanity.* Martha H., æt. 17. Sister insane. Admitted with melancholic symptoms accompanied by considerable mental confusion. Occasionally had to be fed with stomach tube. Could not speak, and it was impossible to determine what delusions were present. After being several weeks in the Asylum she partly recovered, and then relapsed, and there appeared to be considerable mental reduction after the lapse of several months. Then began to brighten, and take more interest in her surroundings, also to gain flesh. The thyroid gland was, apparently, small on palpation. Weight at beginning of the thyroid administration 115 pounds. A single thyroid tablet was administered for ten consecutive days, at the end of which time there was slight febrile reaction, with a pulse ranging from 100 to 110 (normal 78). The mental change was very slight, patient exhibiting some irritability, but nothing more. The weight is now 109 pounds.

On the fourteenth day, the thyroid being continued, the first signs of improvement were noticed. Patient became brighter, ate food without compulsion, and on the twentieth day volunteered to do work about the ward and conversed rationally. The thyroid extract was discontinued on the twenty-second day, and patient was discharged one week later, six months after her admission, and did not relapse.

II. *Melancholia followed by deep dementia.* Olivia P., æt. 27. Education fair. No heredity. Married. Nutrition poor. Thyroid fairly well developed. Weight 100 pounds. On admission refused to speak, and would not take food.

Patient was deeply demented, and quiet for several months before the thyroid treatment was begun. She lost flesh very rapidly, and on the eleventh day of the treatment showed pronounced mental and motor excitement. Slight febrile reaction, accompanied by a pulse rate of 120 beats. On the twelfth day she passed into a state of frenzy, the motor excitement being more pronounced than the mental symptoms. The thyroid extract was now discontinued, but the excitement kept up, despite numerous attempts, with narcotics, baths, and systematic exercise, to allay it, for seven weeks, at the end of which time she died with the clinical evidences of acute miliary tuberculosis. An autopsy was not permitted.

III. *Beginning dementia.* Frank G., æt. 20, well educated, was admitted to the asylum suffering from an attack of acute mania. There he improved, but was taken out too soon, relapsed, was readmitted, and then gradually demented. Thyroid of normal size. Is good tempered. Weight at beginning of thyroid administration 125 pounds. On the seventh day of the treatment became quite irritable and impatient. By the fifteenth day he was so quarrelsome that it was necessary to restrain him. During these 15 days he lost five pounds, and there was considerable tachycardia and sweating. The myxœdematous symptoms were not so pronounced as in some of the other cases. The administration of the extract now being discontinued, he regained weight, became more quiet, and after the lapse of several weeks he was sent to his friends somewhat improved.

IV. *Dementia.* John B., æt. 21, admitted as a case of acute mania, and after a period of four months gradually demented, became quiet, and not at all irritable. Thyroid gland normal. Treatment was now begun, and within a week there was pronounced febrile reaction, with tachycardia and sweating. There is a marked difference in the aspect of the face, which now appears puffed and rounded, in contrast to the former rather emaciated appearance. The facial expression also became anxious, but there was no pronounced excitement. The treatment was continued three weeks longer, without producing other change than an increase of the myxœdematous characteristics, and was then discontinued. From a mental standpoint, the course of the patient's disease was now rapidly downward, and he became absolutely demented and degraded.

V. *Chronic melancholia.* Marcus Z., æt. 30, Russian Jew, admitted to the asylum with alternating melancholia and mania. Thyroid normal. Much emaciated from chronic diarrhœa. Refused food at first. Has been quiet for some months, suffering from well marked delusions of persecution. Under enforced feeding became well nourished, but not less melancholic. Six months after admission treatment with thyroid extract begun. One tablet for ten days, two for four days, and three daily for two weeks longer. On the 11th day became much excited, complaining that his countrymen wished to kill him. There was slight febrile reaction and increase in the pulse rate to 120 (normal 75). The cheeks soon began to assume a marked puffiness, and on palpation had a jelly-like feel. No other phenomena were noticed, except that at the end of the month's treatment he had lost eight pounds, which he rapidly regained after it was discontinued. Then he also became quiet, and at the date of writing still remains an inmate of the institution, retaining his old-time delusions.

VI. *Dementia following puerperal melancholia.* Katie S., æt. 25, was admitted in 1893, four weeks after confinement. Recovered in about six weeks, was taken home, and there relapsed and became permanently demented. Is untidy, mischievous, but never excited. Pulse rate normally 85 to 90. Thyroid normal. Was placed on thyroid extract, one pill, then two pills daily. In second week marked febrile reaction,

pulse 120 to 130, very weak. There is considerable sweating. Facial puffiness well marked. Has become very irritable, restless, and difficult to control. Thyroid extract discontinued after three weeks' administration, after which she gradually returned to her usual condition.

VII. *Deep dementia following confusional melancholia.* Maggie E., æt. 25, was admitted in December, 1893. Thyroid normal. When treatment with the thyroid extract was commenced was untidy and deeply demented. On the tenth day there was slight febrile reaction accompanied by slight motor excitement. These symptoms abated in the course of a few days, though the administration of the thyroid extract was continued, and, after three weeks, no improvement having been noticed, it was discontinued.

VIII. *Imbecility with recurrent mania, followed by apparent dementia.* C. B., æt. 21, admitted with second attack of excitement in December, 1895, and within a few weeks became apparently deeply demented. Thyroid gland very small. Administration of the extract was begun, and after a few days there was febrile reaction, considerable sweating, and a myxœdematous appearance of the integument of the face. The pulse rate altered from 72 to 110, and the patient lost weight rapidly. There were also considerable motor and mental excitement, with the febrile symptoms, all of which gradually abated, though the treatment was faithfully kept up for a considerably longer time. The patient has had several lucid intervals during the fall of 1896, but now seems completely demented.

The above experiment upon eight human subjects points out conclusively that the administration of even the very best and purest of the commercial desiccated thyroid tablets is not unattended by danger to the health and life of the patient, and that at times the administration of very limited amounts of the gland may be followed by symptoms not only difficult to control, but of very marked influence upon the future mental powers of the subject.*

These results obtained, we then decided to further pursue our experiments upon the lower animals, to determine the amount necessary per kilo of weight to cause death, the immediate cause of the dissolution, and the lesions, both macroscopic and microscopic, present at death, especially those pertaining to the cerebrum.

Through the kindness of Dr. Crawford of the Pharmacological Laboratory, who undertook the ordering of the administration to the animals, we obtained material from five mice and three guinea-pigs, to which the same desiccated sheep's thyroid tablets used in the first part of the investigation had been fed; also the cerebrum from one guinea-pig to which had been administered thyroid extract, and the cerebrum of a dog from which the thyroid had been extirpated about one year previous to its death, but in which, at the autopsy, supernumerary thyroids were discovered, though the animal during life had exhibited minor symptoms of a cachexia.

A portion of the material for microscopic examination was hardened in Muller's fluid for after-treatment according to the silver-phospho-molybdate formula, and another portion in alcohol, for staining with the anilines, hematoxylin, and more particularly to examine into the lesions of the blood-vessels, both in the abdominal viscera and cerebrum.

The five mice were first fed with the tablets. All of them ate the pills readily to obtain the sugar coating them. For a few days there was no appreciable effect. Then they grew dull, the cheeks became puffy, there was trembling and increase of the frequency of the respiratory movements, and death rather suddenly.

ABSTRACT OF THE HISTORIES OF THE THYROID MICE.

No. I. Administration of the tablets commenced Aug. 22, '96. One pill 22nd; three, 24th. Animal remains bright and eats other food; 25th, two tablets. On 26th, it seems frightened and the face appears swollen; on the 27th instant, it is still trembling very greatly, and no pill was given. On the 28th, it is very much brighter and the trembling has almost ceased. On the 29th, is bright, and feeding of the thyroid was again begun. Sept. 1st, three pills were fed, the animal eating nearly the whole quantity. The 2nd instant, the face is again swollen, and on the 3rd, refused to eat a portion of the tablets, and has become quite dull. On the 4th and 5th instant, the animal continued dull, trembling, and looks weak and sick. On the 7th, the eyes are very bright, and there is slight emaciation. Five pills were given, but not all were eaten. On the 8th, only two pills were taken; there is much trembling. Died during the night of the 9th instant, having eaten a portion of the tablets left in the cage.

The autopsy showed congestion of all the viscera, but without hemorrhage. The brain was soft.

No. II. On the 22nd August, one pill administered, on the 23rd and 24th, the same quantity, but little not being eaten. On the 25th, two pills were eaten, the animal still remaining bright. On the 26th, two tablets were eaten, and the face shows signs of swelling. On the 27th, the testes have become swollen, in addition to the face, but the appetite is still retained. On the 28th, the eyes are partly closed, and on the 29th, the animal is trembling, the legs are dragged, but it still takes care of its coat.

September 1st, the animal is dull, the face much swollen. Three pills were eaten. On the 3rd, is much brighter, sleeps well, but has not taken all the pills during the last two days. On the 5th instant, will hardly touch the sugar-coated tablet. On the 7th, the face is markedly swollen, the animal is dull, the hair less sleek, and the eyes almost closed. Respiration 134 per minute. Died in convulsions at 2.30 P. M.

The autopsy was performed immediately. Besides some unimportant congestion of the abdominal viscera there were no ascertainable lesions.

No. III. Commenced feeding on 22nd August, but no symptoms were noticed until the 26th, when the face became slightly swollen and the animal declined to eat the pill. On the 28th, there is slight trembling. On the 30th, the trembling continues. On Sept. 2nd and 3rd, took daily three pills. On the 5th, is dull, tottering, very weak. On the 7th instant, the hair is rough, and it seems weak, but eats the pills

*I do not take into consideration the possible presence of putrefactive products in the tablets, as they were perfectly free from all evidences of decomposition.

well. On the 8th, is trembling very much, but eats the pills. Died during night.

Autopsy showed congestion of the abdominal viscera. Brain rather soft.

No. IV. Feeding commenced on August 22nd, but does not eat the tablet well, hardly averaging ¼ of a pill daily. On the 26th, the animal is bright, but the face is slightly swollen. On the 29th, refused to eat pill, but remained dull until September 2nd, and thereafter refused to eat pill at all. On the 12th instant, had apparently fully recovered.

No. V. Administration commenced on the 22nd August, and the dried gland was all eaten. On the 26th instant, the face is swollen. On the 28th, there is much trembling, but three pills were eaten. On the 29th, would not eat pill, but on Sept. 1st ate four pills. On the 5th instant, is trembling considerably, but ate two pills. On 8th instant, was bright, though trembling. On morning of 9th instant, found dead in cage. The autopsy showed the usual congestion.

Abstract of the Histories of the Thyroid Guinea-Pigs.

No. I. Fed with thyroid extract, 20 mg. daily, from Oct. 21st until Oct. 30th, on which day it died. Weight at beginning of experiment, 620 grammes. The animal became dull and gradually emaciated. Weight at autopsy, 380 grammes. All internal organs very much congested. The animal received a total of 180 mg. of extract.

No. II. Pig fed on the same desiccated thyroid as in the former experiments. Weight, 810 grammes. On Oct. 21st, one and a half pills administered; on 22nd, four pills; on the 23rd, the same quantity. The respiration had now reached 144 per minute. On the 24th, 25th and 26th, four tablets were fed daily, and during the night of the 26th, the animal died. At the autopsy the abdominal organs were found to be much congested. Weight, 620 grammes (loss 190 grammes). This animal received about seven grammes of the dried thyroid gland, or less than one per cent. (.864) of its bodily weight to produce a lethal effect.

No. III. Fed on desiccated thyroid tablets. Weight, 580 grammes. Oct. 21st, one pill; on 22nd, three tablets; on the 23rd instant, four; on the 24th, 25th and 26th, the same; on the 27th instant, six pills; on the 28th, four tablets; on the 29th, five; on the 30th, five. The animal had been for several days very dull and had rapidly emaciated. The exitus took place on the morning of the 30th instant. At the autopsy the viscera were found to be much congested. The weight was 320 grammes. Loss of weight during the nine days of the experiment, 260 grammes. The animal received more than 2 per cent. of its weight in the dried gland to produce dissolution.

No. IV. The same thyroid preparation fed. Weight at beginning of the administration, 610 grammes. On Oct. 22nd, two tablets were fed to the animal; on the 23rd, three; on the 4th, four pills; on the 26th, six pills; on the 27th, four pills; on the 28th, five pills. The pig has become very dull and does not take care of its fur. Died Oct. 30th. At the autopsy the animal weighed 370 grammes (loss, 240 grammes) and the viscera were much congested. This animal received 1.30 per cent. of its bodily weight of the gland to cause death.

No. V. Thyroid dog (Dr. Abel). Thyroid gland extirpated *in toto* in Oct. 1895; died one year later, after showing profound emaciation and a dermatitis suggestive of myxœdema. At the autopsy several parathyroid bodies the size of a small pea were discovered. This animal was fed for several months on thyroids and thyroid extracts, seemingly without benefit. The autopsy showed no demonstrable lesions.

The guinea-pig series may be looked upon as an example of the acute type of poisoning by the administration of thyroid gland, while the mice are of a more chronic order. It is impossible to estimate the exact percentage necessary to produce lethal results with the mice, for the reason that these small animals always left some crumbs of the tablets on the floor of their cages which it was not practicable to collect. The guinea-pigs on the other hand were fed with the entire pill without loss, and but in one case was less than about one per cent. of desiccated gland found to produce lethal results, the administration being distributed over five days.

The microscopic examination of the cerebra of the eight mice and guinea pigs showed, both with the silver phosphomolybdate, and aniline and hematoxylin stains, an absolutely normal condition of the nerve elements and neuroglia; none of the varicose and atrophied dendrites, with loss of the gemmulæ, of the former studies being discovered. The corpora retain their angularity and sharp outlines, and the axóns with their appendages, the collaterals, retaining their natural appearances. The sections stained with anilines and hematoxylin showed the normal appearances of the nucleus and nucleolus, and not even in the tunics of the blood-vessels, where pathological changes were most carefully sought for, could any demonstrable lesion be discovered.

The nearest approach to any pathological condition found was in the cerebrum of the dog that had had its thyroid gland extirpated a number of months before death, though even here the lesions were confined to a very few tumefied dendrites, a condition that was most probably caused by the long continued state of mal-nutrition into which the animal had fallen.

More particular attention was paid to the examination of the liver than to the other organs of the abdominal cavity, but here again we failed to find more than a turgescence of the blood-vessels, the liver cells retaining their natural characteristics.

It is obvious from these results that the death of the various animals was induced by an entirely different kind of intoxication than that causing the lesions of the nerve elements in ricin and alcohol toxæmias, and it is therefore a poison that does not induce degenerative alterations in the sheaths of the arteries, and the consequent disturbance of the nutritive supply, followed by pronounced changes in the neurôns, dependent to a certain degree upon the intensity of the vascular lesions; but acts upon the general system in an entirely different manner, and is essentially more subtle in its effects upon the nerve tissues, corresponding more to the action of a group of chemical poisons that leave no trace of their effect after death upon the nerve cell, but during life inducing symptoms directly referable to the central nervous system. The tissue metabolism induced by the action of these poisons upon the nerve cell we can only at present conjecture.

FIVE SUCCESSFUL CASES OF GENERAL SUPPURATIVE PERITONITIS TREATED BY A NEW METHOD.*

BY J. M. T. FINNEY, M. D., *Associate Professor of Surgery, The Johns Hopkins University.*

Recovery following laparotomy for purulent peritonitis is unfortunately of sufficient rarity to excite interest whenever it occurs. My object in making this report to the Society is two-fold; first, to record five successful cases of laparotomy for general suppurative peritonitis, all treated by the same method; and second, to describe briefly the method itself. The principle involved is not a new one; only in the manner of carrying it out is there any originality claimed.

Since the appearance in 1877 of the classical work of Wegner, and later that of Grawitz and others, it has been known that the healthy peritoneum is capable of disposing of a considerable amount of infectious material. J. G. Clark, in a recent article,† reviews the literature of the subject and gives the conclusions reached by the experimenters in this direction. All agree that the peritoneum is able under favorable conditions to take up a relatively large amount of infectious material and dispose of it effectually. These observers were dealing with a more or less healthy peritoneum. On opening the abdomen of a patient suffering from general suppurative peritonitis, however, we have very different conditions with which to deal. The observations of Pawlowsky would indicate that the lymph channels leading from the peritoneal cavity are choked with infectious bacteria and inflammatory products in purulent peritonitis, and that thus the efficiency of the peritoneum would be greatly impaired. Our observations clinically seemed hardly to bear this out.

The question that suggested itself to our mind was this, whether or not the peritoneum, even under these most unfavorable conditions, still retained its absorptive power. It seemed to us, from our experience in operating upon such cases by the methods heretofore employed, that they were inadequate and did not remove a sufficient quantity of the exudate, but left the peritoneum little better off than before. With this idea in mind we devised a plan of treatment which, so far as we know, has not been employed elsewhere.

The steps of the operation are as follows: Make a sufficiently long incision to admit of easy access to all parts of the peritoneal cavity. Quickly withdraw the coils of small intestine from the peritoneal cavity, beginning with the worst coils first. Remove all, or as much as is necessary of the small intestine and place it outside the abdomen, covered with warm gauze or towels, thus practically disemboweling the patient for the time being Then thoroughly and systematically wipe out the peritoneal cavity with large pledgets of gauze wrung out of hot salt solution, paying particular attention to the pelvic portion. In some cases it may be well in addition to flush out the cavity with warm salt solution, but this is rarely necessary.

Next the small intestine should be systematically examined loop by loop while still outside the abdomen, and rendered macroscopically clean by wiping with gauze compresses wrung out of hot salt solution. It is necessary to wipe with considerable force at times, in order to remove adherent flakes of partly organized lymph. It should be done thoroughly and conscientiously, however, as upon this depends, we believe, in great measure, the success of the operation. It facilitates the cleansing process, as well as lessens the shock of the operation, if the wiping of the intestinal coils is carried on under a constant irrigation of warm salt solution.

After being cleansed macroscopically of all foreign material, pus, feces, lymph, etc., the intestine should be replaced in the abdomen—the worst or sutured coil being the last, or most superficial, in order that it may be the better drained by being packed about with gauze, if necessary.

The abdominal wound is then tightly closed, leaving just room enough between two sutures for the gauze drain. If there are any evidences of distension or pain the abdomen should have the Paquelin cautery thoroughly applied, and the bowels moved early by calomel in broken doses, followed by salts and a turpentine enema.

It is not claimed for this method that it will cure every case of general suppurative peritonitis. We believe, however, that a larger percentage of cases will recover after this method than any other with which we are familiar.

To insure success with any method it is essential that the operation should be performed within a few hours after the perforation has taken place. This is well brought out in the very interesting series of experiments on dogs made for me by Messrs. Elting and Calvert of the Johns Hopkins Medical School, a report of which is subjoined.

Five cases have been operated upon by this method up to date, all of which have recovered. The first case, a case of perforating typhoid ulcer, has already been published,* and hence only a very brief abstract of the history will be given here.

CASE I.—Male, aged 47, on about eighth day of mild attack of typhoid developed symptoms of perforation. Entered hospital 14 hours later and was operated upon immediately. Peritoneum everywhere intensely congested, roughened and dull, and covered with flakes of plastic lymph. Considerable amount of turbid purulent fluid in abdominal cavity. Perforation in ileum about 14 inches from ileo-cæcal valve. Fecal matter exuding from opening. Peritoneum cleansed in the manner described, gauze drainage. Recovery.

CASE II.—G. W., male, aged 20. Saw patient for the first time, November 24, 1896, in consultation with Dr. Barringer in Charlottesville, Va. Patient gave history of four previous mild attacks of appendicitis, from which he had promptly

*Read before the Medical and Chirurgical Faculty of the State of Maryland at its Annual Meeting in Baltimore, April 27, 1897.

†Bulletin of the Johns Hopkins Hospital, April, 1897.

*Annals of Surgery, March, 1897.

recovered. The night before he had eaten very heartily of apples. He was awakened about 3 a. m. with severe abdominal pain, cramp-like in character. At about 6 a. m. Dr. Barringer was called. He stated that at this time, three hours after the beginning of the attack, the patient presented the classical symptoms of peritonitis. When I saw him, 24 hours later, he had a temperature of 102° and a pulse of over 100, and from the first had suffered intense pain, which was controlled only by morphia hypodermically. He had had nausea and vomiting all day. Examination of the abdomen showed slight distension and great rigidity of the abdominal muscles. A slight tumefaction could be made out just to the inner side of the anterior superior spine of the ilium on the right side. Tenderness very marked. Immediate operation advised and agreed to. Incision 5 inches long in right linea semilunaris. On opening the peritoneal cavity the intestinal coils in the right lower quadrant of the abdomen were found to be congested and dull and covered with flakes of adherent lymph. Elsewhere the intestinal coils were found to be congested, but not otherwise much changed in appearance. The pus, of which there was perhaps 200 cc., was not walled off, but everywhere present in pockets between the adherent intestinal coils. The appendix was readily found. It was closely adherent to the pelvic brim on the one side and the cæcum on the other. Its distal end was swollen and distended to the size of my thumb, perforated and gangrenous over an area about as large as a five-cent piece. Appendix was ligated and excised, and stump covered with peritoneal cuff and suture. The peritoneum was treated in the manner above described. Recovery.

Case III.—This patient was seen first on December 14, 1896. His history is in brief as follows: R. S., male, aged 33 years. Has had no previous similar attack. The night before he was taken sick he attended a banquet and ate heartily of solid indigestible food. He was attacked with severe abdominal pain about 3 o'clock the next afternoon. The pain at first was general and cramp-like; nausea and light vomiting during the night. Morphia was necessary to relieve him. The next day he was unable to get up. Toward evening his physician gave him a cathartic, after which the bowels moved 8 or 10 times in quick succession. The next morning the pain had shifted to the right side and was severe. He received a hypodermic of morphia and got on fairly well until about 6 p. m., about 60 hours after the onset of the attack, when he was taken with a sudden severe pain in the lower right side of the abdomen. The pain for a time was excruciating at the base of the penis. Vesical and rectal tenesmus marked. When I saw him, about 4 hours later, in consultation with Dr. Reiche, he had a temperature of 105° and pulse of 150, profoundly collapsed. I have never seen such a hard and retracted abdomen as he presented. His condition appeared grave. Immediate operation advised and consented to.

Incision about 5 inches long, in right linea semilunaris. On opening abdomen the intestinal coils were found not to be distended but considerably congested. Beginning in the right lower quadrant there was found a considerable amount of thin pus containing flakes of lymph. This condition extended over into the left side, down into the pelvis and up into the hypogastric region. The appendix was found to be gangrenous and perforated, and was removed. The toilet of the peritoneum was made in the manner already described, by disemboweling and vigorously scrubbing the parietal and visceral peritoneum until macroscopically clean. The intestinal coils were then replaced, a gauze drain inserted, and the abdominal wound closed except a small opening for the drain. He made an uninterrupted recovery.

Case IV.—M. B., boy, aged 10. Operation by Dr. J. C. Bloodgood, January 7, 1897. Five days before admission to the hospital was struck in the abdomen by the fist of a playmate. Next day felt severe pain in the right iliac region. This progressively increased for three days, when vomiting began and the pain became general. Two days later was brought to the hospital, when his condition was found to be in brief as follows: Temperature 101°, pulse 128 and fairly good. Slight abdominal distension. Muscular spasm marked on right side, present but less marked on the left. General abdominal tenderness. Under ether a definite tumefaction could be made out in the region of the right kidney. This proved to be an abscess behind the cæcum, extending from the iliac fossa below to the liver above, and in this cavity was the diseased appendix. There was found no walling off of this from the general peritoneal cavity. The entire pelvis was filled with yellow pus and all the intestinal coils were covered with flakes of fibrin. The stomach and spleen were not seen, but the surface of the liver looked exactly as if it had been covered with yellowish-white paint. The appendix was removed and the entire abdominal cavity thoroughly wiped out with gauze pledgets wrung out of salt solution. The exudate was scrubbed off the liver's surface, after which it looked simply congested. A gauze drain was inserted and the abdominal wound partly closed. He made an uninterrupted recovery. Cultures and cover-slips from the peritoneum showed colon bacillus and a coccus (not differentiated).

Case V.—R. S. P., aged 9, a schoolboy, entered the Johns Hopkins Hospital, Feb. 26, 1897. He had always been healthy except for measles, whooping cough and chicken-pox.

Family history good except remote cases of tuberculosis on both sides.

Just 48 hours before entering the hospital first complained of pain in abdomen. Three hours later had an attack of vomiting. Pain in abdomen was at first general, but in a few hours became localized in the right iliac and lumbar regions. After about 24 hours the pain lessened somewhat, and he sat up for a little while, but shortly after pain and vomiting returned with increased severity. A physician saw him after about 36 hours and gave him calomel in broken doses. His bowels moved twice. His condition did not improve, and by advice of his physician was brought to the hospital at 8 p. m., 48 hours after the onset of the attack. His condition then was as follows: Face flushed and anxious. Pulse 126; temp. 102.8°; resp. 56, and entirely thoracic; abdomen generally distended and tender, especially in right iliac fossa, where the tenderness is extreme and muscle spasm very marked. Pain is most marked here also. Liver and spleen not palpable. Liver dullness on right corresponds about to costal border.

Percussion over right iliac and lumbar regions shows dullness; tympanitic over left side. Heart normal. Fine moist râles over bases of both lungs. No history of any similar previous attack.

Diagnosis.—Perforating appendicitis with beginning general peritonitis. Immediate laparotomy advised and agreed to. Ether. When thoroughly anæsthetized, a small, hard mass, somewhat movable, could be felt just over the middle of Poupart's ligament. An incision about 15 cm. long was made parallel to and over the right linea semilunaris. After exposing the peritoneum and before opening it several bubbles of gas could be seen free in the peritoneal cavity. On opening the peritoneum a considerable amount of thin, cloudy seropurulent fluid escaped and some gas. The mass felt before was found to be the appendix with a roll of omentum adherent. The intestines, especially the cæcum, were distended and congested, and covered with flakes of fresh fibrinous exudate. The congestion was most marked in the immediate vicinity of the appendix.

The appendix itself was superficially placed and freely movable, not walled off, but had a portion of omentum adherent. It was rather long, and curled upon itself, with a constriction at about the junction of its proximal and middle thirds. It contained two concretions, the larger of which was engaged tightly in the constriction, and from this point to the tip the appendix was gangrenous and softened. A small perforation was present at the distal end of the date-seed like concretion. There had been an apparent attempt of the omentum to surround the entire gangrenous end of the appendix, but it had not quite succeeded. The appendix together with the adherent omentum was ligated and excised.

Pelvis was found to be full of pus, and the peritoneum treated as above. He made a rapid and complete recovery.

Bacteriological examination of the peritoneal exudate showed the presence of streptococcus, staphylococcus, and bacillus coli communis.

NOTE.—Since reading the above article, I have operated upon one additional case of general peritonitis. The patient, a young woman, was *in extremis* at the time of the operation, which was undertaken simply as a forlorn hope. This operation was secondary to one performed several days previously by another surgeon for appendicular abscess. There was found present a general peritonitis, with much plastic lymph covering the greatly distended and adherent coils of intestine. There was very little purulent fluid in the abdomen. Her pulse was very rapid and thready, and her temperature had risen several degrees. After the operation she was placed in a continuous bath, which added greatly to her comfort. The operation seemed to prolong her life, as she lived about thirty-six hours following it.

AN EXPERIMENTAL STUDY OF THE TREATMENT OF PERFORATIVE PERITONITIS IN DOGS BY A NEW METHOD OF OPERATION.

BY ARTHUR W. ELTING AND WILLIAM J. CALVERT.

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At the suggestion of Dr. Finney and with the permission of Prof. Mall, the writers have undertaken an experimental study of perforative peritonitis in dogs, with especial reference to the method of treatment of this disease in human beings, introduced by Dr. Finney. Inasmuch as this is a preliminary report, the literature upon the subject will not be considered. It may be mentioned, however, that so far as we know no previous work of this nature has been done from a surgical standpoint. It was decided to divide the series of experiments into four groups:

1. To scrub the intestines of a series of normal dogs and study the condition of the abdominal cavity at varying lengths of time after the operation, in order to determine the results of the mechanical irritation.

2. To determine how long it takes a perforative peritonitis to destroy life.

3. To perforate the intestines of a series of dogs, and after varying lengths of time to operate upon them again, closing in the perforation and cleansing the abdominal cavity and the surface of the intestine and mesentery, and after variable periods of time to kill the dogs which recovered, and study the condition of the abdominal cavity.

4. To perforate the intestines of a series of dogs, and after varying lengths of time to close in these perforations without removing from the abdominal cavity any of the exudate or foreign matter present, and to study the results of this operation.

The dogs used in these experiments varied in weight between 18 and 52 pounds, most of them weighing about 25 pounds.

For the first group of experiments four dogs were used. By a median incision the abdominal cavity was opened, the intestine and parietal peritoneum were vigorously scrubbed with gauze sponges wrung out in warm normal salt solution, and kept covered with warm towels. After this treatment numerous minute hemorrhages caused by the scrubbing were noticed over the peritoneal surfaces, and the intestine presented an extremely congested appearance. It was then thoroughly irrigated with warm normal salt solution, which had a marked effect in reducing the congestion. The intestine was then replaced in the abdominal cavity and the wound closed. The process of scrubbing as performed by the operator and an assistant required from 8 to 12 minutes. In every case the dog appeared ill for about 24 hours after the operation, after

which a marked improvement in the condition was noticeable. Usually by the end of the second day the animal seemed quite well.

Of these four dogs one was killed by an accident one day after the operation. Autopsy showed a very small amount of blood-tinged serum in the abdominal cavity. The surface of the intestine and parietal peritoneum presented numerous hemorrhagic areas caused by the scrubbing at the time of operation. The surface of the intestine was roughened, though not adherent. Cultures from the abdominal cavity were sterile.

A second dog was killed at the end of three days. At autopsy no appreciable amount of fluid was found in the abdominal cavity. Numerous fibrinous adhesions of the coils of intestine to each other, to the inner surface of the abdominal wound and to the omentum were found. The surface of the intestine was slightly roughened and presented numerous hemorrhagic areas. Similar areas were also seen upon the mesentery near its attachment to the intestine and upon the parietal peritoneum. These were likewise caused by the scrubbing at the time of operation. Cultures from the abdominal cavity were sterile.

A third dog which was in excellent health and condition was autopsied at the end of five weeks. No appreciable amount of fluid was found in the abdominal cavity. The appearance of the organs was everywhere normal except for numerous adhesions of coils of the intestine to each other, to the omentum, to the inner surface of the abdominal wound and to the stomach. These adhesions were of a firm character, being apparently composed of fully developed connective tissue. Cultures from the abdominal cavity were sterile. The fourth dog is still alive and will be autopsied later. From this group of experiments we conclude that mere mechanical irritation may cause the formation of extensive adhesions in the abdominal cavity of the dog, but these seem in no way to seriously interfere with the animal's general health.

For the second group of experiments four dogs were used. Because of its accessibility and the comparative ease with which the perforation could be closed, it was decided to perforate the cæcum. By the use of a stick of caustic potash a perforation 1½ cm. in diameter was made in the end of the cæcum, after which it was replaced in the abdominal cavity and the abdominal wound closed. These dogs showed symptoms of a severe peritonitis and died in from 12 to 20 hours from the time the perforation was produced. Autopsy showed practically the same pathological condition in each case. From 150 to 250 cc. of a turbid bloody fluid were found in the abdominal cavity. The surface of the intestine presented a marked hemorrhagic condition, both diffuse and petechial in character. The omentum, mesentery and parietal peritoneum presented a similar appearance. Flakes of reddish yellow lymph were deposited over the surface of the viscera, particularly in the region of the liver, diaphragm and lesser omentum. Slight fibrinous adhesions between the coils of intestine were noted. The mucosa of the intestine presented more or less of a hemorrhagic appearance, and in some of the cases bloody contents were found in the lumen of the gut. In short, the pathological condition was one of an intense hemorrhagic peritonitis associated with a more or less extensive hemorrhagic enteritis. The bacteriology of each of these cases was carefully worked out and will be referred to later.

For the third group of experiments twelve dogs were used. The method of operation was as follows: An incision was made on the right side just outside the rectus muscle, the cæcum brought out and perforated in the same manner as practiced in the experiments already described. The cæcum was then replaced in the abdominal cavity and the abdominal wound closed. From five to seven hours after the perforation was produced these dogs were again opened by an incision in the median abdominal line. The perforated end of the cæcum was brought out and the perforation closed by means of a row of mattress sutures, after the necrotic tissue at the seat of the opening had been resected. The abdominal cavity was then opened, and the intestines being lifted out, were kept carefully covered with towels wet in warm normal salt solution. With gauze sponges wrung out in this solution the surface of the intestine and mesentery was carefully wiped till it appeared macroscopically clean. The abdominal cavity was next wiped out and rendered macroscopically clean, the intestine in the meantime being frequently irrigated with warm salt solution and kept covered with warm towels. After another thorough irrigation of the intestine with the warm salt solution it was replaced in the abdominal cavity and the wound closed in the usual manner. We cannot emphasize too strongly, in doing these experiments, the advisability of thorough and constant irrigation of the intestine while it is outside the abdominal cavity, for in every case it seemed to reduce the congestion and in some cases the distension. The cleansing process required from 10 to 20 minutes according to the amount of exudate and foreign matter present.

Of these 12 dogs one was operated on at 5 hours after the perforation was produced, one at 5¼ hours, one at 5½ hours, one at 6 hours, two at 6¼ hours, three at 6½ hours, one at 6¾ hours, one at 7 hours, and one at 7¼ hours.

In every case the dog showed marked symptoms of peritonitis and evidences of pain. When lying down the legs were drawn toward the abdomen, which was held very tense. Any attempt to straighten out the legs seemed to cause great pain. In some cases the dog vomited a somewhat bile-stained fluid. In every case the abdominal cavity at the time of the second operation contained from 100 to 250 cc. of a turbid bloody fluid. The intestine, mesentery and omentum in nine of these cases presented a generalized hemorrhagic condition. In the remaining three cases this condition seemed more confined to the coils of intestine in the region of the cæcum, though all the peritoneal surfaces seemed more injected than normally. In nine of the cases more or less numerous flakes of yellowish red lymph were found adherent to the gut, mesentery, greater and lesser omentum and other abdominal viscera. In eight of the cases the intestines seemed more or less distended when replaced in the abdominal cavity, Immediately after the cleansing of the surface of the intestine and the abdominal cavity the animals seemed to be much more comfortable, and in the case of every dog which recovered there was a progressive improvement in the condition.

In no instance did a dog which recovered show signs of

pain after the cleansing operation was performed, and usually in from two to three days the dog seemed to have recovered completely from the peritonitis, so far as external symptoms would indicate. Of course the abdominal wound made at the second operation was infected, and this in nearly every case failed to heal by first intention, which delayed somewhat the complete recovery of the animal. Of the 12 dogs thus treated three died without any apparent beneficial effect of the operation, death ensuing within 20 hours from the time the perforation was produced. These three dogs were operated upon 6¼, 7 and 7¼ hours respectively after the perforation was produced. A fourth dog operated upon 6½ hours after the perforation died 30 hours later; the operation apparently prolonged its life about 20 hours. In three of these cases the peritonitis was the most severe we met with in our experimentation, and the dogs in a weak condition at the time of operation, which was done comparatively late in the disease. In each of these four cases the intense hemorrhagic peritonitis described under the second group of experiments was found at autopsy.

The remaining eight dogs were apparently cured of the peritonitis. Of these eight, one died from the protrusion of the intestine, due to the breaking down of the abdominal wound on the fifth day after the operation. In a second case death resulted on the eighth day from a localized peritonitis due to the extension of the suppurative process from the abdominal wall. A third dog which appeared quite well 2½ days after the operation died rather suddenly on the fourth day from a perforation in another portion of the intestine which had come into contact with the caustic potash upon the end of the perforated cæcum at the time the first perforation was produced. A fourth dog appeared quite well at the end of twelve days after the operation, having an excellent appetite and seeming very lively. On the 13th day the dog seemed sick, and gradually grew worse till its death, on the 17th day after the perforation was produced. At autopsy small abscesses were found extending along each stitch in the abdominal wall down to the inner surface of the wound, where the intestines and omentum were adherent. No distinct sinus leading into the abdominal cavity could be demonstrated. The abdominal cavity contained about 100 cc. of yellow pus, collected for the most part in the pelvis and also extending up toward the diaphragm. The coils of intestine and omentum were firmly adherent in a mass in the upper part of the abdominal cavity. The intestine was also adherent to the liver and gall bladder. The parietal and visceral peritoneum were intensely hemorrhagic in places. No apparent walling off of the pus existed. An extension of the suppurative process along the stitches was supposed to have been the source of the infectious material. A fifth dog also apparently made a complete recovery, both wounds healing with the exception of a small sinus in one of them. This dog seemed quite well for nearly three weeks, when it became ill and died three weeks and two days from the time it was operated upon. At autopsy the abdominal cavity presented a perfectly normal appearance, with the exception of numerous adhesions of coils of the intestine to each other, to the omentum, liver and parietal peritoneum. These adhesions were not very firm in character. The sinus mentioned above was found to lead to an abscess cavity about the size of a hen's egg, situated in the pelvis to the right of the uterus. This abscess was completely shut off from the rest of the abdominal cavity and was the undoubted cause of death.

All of these dogs which died as a result of the suppurative process following the operation would probably have recovered could they have been subjected to the same treatment human beings would receive in a similar condition, for it must be remembered that it is practically impossible to drain or treat suppurating wounds in dogs. A sixth dog, apparently in the best of health and condition, was killed and autopsied four weeks after operation. Both wounds had healed with the exception of a small sinus leading to a stitch abscess, which, however, did not penetrate the abdominal wall. On examining the abdominal cavity the only abnormalities noted were seven or eight slight, loose adhesions between coils of the intestine, three or four loose adhesions of the omentum to the intestine, and some rather firm adhesions of intestine to the inner surface of the abdominal wound over an area 3x6 cm. The condition of the viscera seemed everywhere normal. All of the adhesions, except perhaps those uniting the intestine to the inner surface of the abdominal wound, were of such a slender character that they would in all probability have disappeared entirely in a few months. The remaining two animals are apparently perfectly well, one of them being a bitch which was in a moderately advanced state of pregnancy when operated upon. Cultures and cover-slips were made from the exudate in each case of peritonitis. The bacteriology was carefully worked out and will be referred to later. From this group of experiments we conclude that up to 6 hours after perforation the generalized peritonitis in dogs can be cured by this operation in practically every case. The prognosis of operation upon these animals at 6½ hours after perforation is exceedingly favorable, but from that time on rapidly becomes less favorable.

For the fourth group of experiments six dogs were used. The method of procedure in this group was to perforate the cæcum in the usual manner. From 6 to 6½ hours later the abdominal cavity was again opened, the cæcum brought out and the perforation closed in the way before described. After the replacement of the cæcum the abdominal cavity was closed without in any way attempting to cleanse it. At the second operation four of these dogs presented a generalized peritonitis with the characteristics before described, though in no case did the condition seem as bad as in the cases of two dogs in Group 3 cured by the cleansing of the surface of the intestine and the abdominal cavity. Of these four dogs one died about 20 hours after the perforation was produced. The other three failed to rally after the second operation, as the dogs in Group 3 did, and appeared ill till their death two to three and one-half days from the time the intestine was perforated. Autopsy upon two of these animals showed an intense hemorrhagic peritonitis, while in the case of the third the intestine and omentum were closely adherent in a mass, which when pulled apart disclosed numerous pockets of pus, presenting the condition of multiple abscess formation. The remaining two dogs of this series presented only a localized

peritonitis. There was not more than half as much of the turbid bloody fluid in the abdominal cavity as found in the other four cases, and only those coils of intestine in the vicinity of the cæcum presented a hemorrhagic appearance. These were the most favorable cases we met with in all our experimentation. These two dogs are still alive, though their recovery has been slow.

In connection with the last two cases it is interesting to note that in two of the cases of Group 3 some exudate had collected in the abdominal cavity between the time the intestine was replaced and the abdominal wound closed, thus making it evident that the abdominal cavity possessed the power of caring for a considerable amount of the exudate. The bacteriology of this group of experiments was also carefully worked out and will be referred to along with the reports of the other cases of peritonitis.

This group of experiments seems to demonstrate that the mere closure of the perforation, though it may in some cases prolong life slightly, is not sufficient to cure a case of generalized peritonitis in dogs, and makes it very evident that without a careful cleansing of the surface of the intestines and the abdominal cavity recovery in such cases will be exceedingly rare. It must be borne in mind that the length of time which had elapsed since the perforation was produced and the condition of the abdominal cavity would have afforded a most favorable prognosis in these cases had the cleansing operation been performed.

Cultures were made from the 4 cases of Group 2, 12 cases of Group 3, and 6 cases of Group 4. In one case of Group 3 the cultures failed to grow, although cover-slips showed a few cocci and bacilli. Also in one case of Group 4, in which the peritonitis was not yet generalized, the cultures were negative. In the twenty cases in which bacteria developed in the cultures, from one to three species of microorganisms were found in each case. Members of the colon group were found 18 times, 4 times alone and 14 times in association. Streptococcus pyogenes was found 8 times, once alone and 7 times in association. Staphylococcus albus was found 5 times, in each case in association. Staphylococcus aureus was found 4 times, once alone and 3 times in association, and staphylococcus citreus was found 4 times, in each case in association. Cultures were also made from the heart blood at several of the autopsies, but in each case were sterile. Cover-slips from the exudate in the abdominal cavity were examined in each case and more or less numerous bacteria were seen. An abundance of leucocytes was found in nearly every cover-slip. The bacteria in general were outside the cells.

From our experimental work we feel justified in stating the following conclusions:

1. That mere mechanical irritation of the peritoneal surfaces will lead to the formation of adhesions.

2. That peritonitis in dogs caused by a perforation of the intestine is of an intensely hemorrhagic character, and if left to itself rapidly proves fatal.

3. That generalized peritonitis of this character, in dogs, can be cured as late as 6½ hours after the perforation, by the cleansing operation introduced by Dr. Finney.

4. That mere closure of the perforation without this cleansing operation will rarely, if ever, cure a case of generalized peritonitis in dogs.

SQUAMOUS EPITHELIOMA AND EPITHELIAL HYPERPLASIA IN SINUSES AND BONE FOLLOWING OSTEOMYELITIS.

By S. M. Cone, M. D., *Assistant in Surgical Pathology, The Johns Hopkins University.*

In view of the interest manifested in the pathology of bone, the two cases about to be reported seem to be of value. They are striking examples of malignant and benign epithelial growth into old sinuses and medulla of bone.

Case I.—John H., colored, æt. 45, laborer, was admitted to Dr. Halsted's wards, January 2, 1897.

Patient gives a history of injury to his left tibia 19 years ago, with subsequent formation of a sinus and discharge of sequestra. One month before entering the hospital the patient began to feel pain in the leg, and the odor of the discharge became foul. No sequestra have come away for eight months. There is pulsation of discharging material synchronous with the radial pulse.

Upon Jan. 4, Dr. Bloodgood excised the sinus and chiseled and curetted the bone. The bone was fractured 10 cm. below the knee, where the cavity was largest. The operator's note estimates the cavity communicating with the sinus as 3 cm. deep, 2 to 3 cm. wide, and 14 cm. long. The diagnosis, squamous epithelioma, being confirmed, and the growth recurring within two weeks, the leg was amputated above the knee, and glands of the groin excised by Dr. Finney on Jan. 29th. On Feb. 25th patient was discharged, the wounds having healed *per primam*.

Pathological report of the first operation.—The specimen consists of the skin, sinus, eburnated bone, and soft material filling the cavity in the bone. The edges of the sinus are dense and pearly in appearance. The skin within ½ cm. of the sinus edge has lost its dark pigmentation. The bone next to the soft central mass is soft and crumbly, but outside of this is eburnated. It appears directly continuous with the skin at the orifice of the sinus. The sinus is lined by the same papillary growth that fills the cavity in the bone, and this same growth projects between the periosteum and eburnated bone, indenting it, causing a jagged appearance. The medullary cavity is filled with a soft, necrotic-looking material, made up of soft yellowish white masses, and with white papillary granular projections from a rather dense translucent pink ground substance looking like granulation tissue. The papil-

lary projections average 2 mm. diameter, and are of varying length up to 4 mm. The growth within the cavity erodes the bone, leaving small spicules and granules in the soft necrotic mass. In places the dense bone has become granular and crumbles readily. There is no sequestrum nor cancellous bone. The periosteum is very much thickened and not to be well differentiated from the subcutaneous tissue; it is invaded by the epithelial growth. The microscopical description of the original sections is the same as of the recurrent growth, so they will be included together.

The leg and lower third of the thigh removed at the second operation present no abnormal appearance outside of the gaping granulating wound in the tibia, the seat of an osteotomy performed January 4th. The wound, measuring 16x 4x4 cm., is surrounded by edges of skin inverted over the bone, which for the most part is covered by apparently healthy granulations. Only at one place is the bone exposed; this is at the upper angle of the wound, where an edge of eburnated bone is left uncovered. At the outer rim of the excavated tibia, 4 cm. from the upper angle of the wound, is a projecting mass of papillary excrescences 4 cm. in diameter, whose surface is covered by a dry blood-stained crust. Scraping the upper layer away leaves the deeper papillæ, pearly in appearance, closely aggregated and more or less intimately connected with the velvety granulations about them. Some of these epithelial nests are so closely packed without any apparent stroma that at first glance they give the appearance, on section, of a cheesy mass. Careful observation shows this to be made up of individual nests. This mass is at the seat of fracture alluded to. Similar nests of cells are seen in smaller discrete masses over the whole surface in the granulations.

One area on the inner wall of the excavated tibia, 5 cm. from the upper angle of the wound and 2 cm. from the fracture, can be made out as a mass sharply defined from the surrounding granulations. The bone here seems excavated to fit the growth which is eroding it. Spicules of bone project into the growth between the epithelial plugs at the periphery. Between the ends of the fracture the new growth projects, invading muscle and adjacent tissues. The ends of the bone are rough, and the papillary masses are seen indenting the ivory-like bone to a depth of 1 to 3 mm., giving it a worm-eaten appearance on removing the growth. The granulations, 2 to 4 mm. thick, covering the surface of the bone also groove it and cause a rough and gnawed appearance.

The bone sawn through at several places is dense and eburnated and shows no evidence of tumor formation which is not directly connected with the surface growth. The heads of femur, tibia and fibula and the astragalus are normal. The tibia and fibula are anchylosed by bony union at the interosseous ligament. No tumor can be traced from the bone along the vessels. The muscles and soft parts, except at the seat of fracture and ulcer edge, appear normal. The cartilage of the patella is softened, that over the outer head of the femur is depressed and soft. The synovial membrane is hemorrhagic where it envelops the crucial ligaments at their insertion into the head of the tibia.

The popliteal and inguinal glands are firm, enlarged and harder than normal, but do not show any areas of metastasis.

MICROSCOPICAL DESCRIPTION.

Tumor invading muscle at the seat of fracture. The tumor mass is sharply circumscribed. At that part nearest the invaded tissue the tumor is made up of single cells and small masses of cells in a fine reticulum; this passes, further away, into small non-cornified, non-cystic masses of cells, then larger alveoli with cornified epithelium in the centre of the stratum mucosum layers. Furthest away from the muscle and nearest the periphery of the tumor mass are seen cystic dilatations with anastomosing alveoli lined by a few layers of columnar cells and containing scales of cornified epithelium and fatty detritus. The invaded fibrous tissue shows no change. The muscle fibres are granular and fragmented; the fragments and individual fibres contain many nuclei, giving the appearance of elongated giant cells. The vessel walls show round cell infiltration. There are newly formed capillaries among the degenerating fibres. There is evidence of endothelial proliferation in the capillaries.

Tumor mass and skin, the mass projecting between the fractured ends of the tibia. Where skin and tumor pass over into one another the regular papillæ of the skin cease, as does the deep pigmentation. The pigment is no longer seen between the stratum mucosum cells as in the skin, and is much less developed in the stratum granulosum and deepest columnar epithelium of the Malpighean layer.

It looks as if the stratum mucosum and granulosum were continuous with like layers of cells lining the stroma of the tumor, keeping on over the tortuous papillary bulgings and corresponding depressions of the tumor mass. Similarly can the stratum corneum be followed, but it changes its appearance over the tumor, becoming less compact and scattered in flakes on the surface, or loosely filling cystic cavities along with cellular detritus, or it may be lacking on some of the plugs.

In the cornified layers over the tumor are masses of brown granular pigment containing crystals of hæmatoidin. The tumor growth is divided by deep grooves caused by keratinizing and fatty degeneration of epithelial down-growths. This causes the follicular appearance described macroscopically.

Papillæ, or stroma strands, better named, push the epithelium up into bulging papillary masses. These stroma strands vary in size, as do the corresponding cylinders and plugs of epithelium lining them. The plugs and cylinders anastomose freely at the surface. One cyst thus caused measures $1 \times \frac{1}{2}$ cm. and is made up of numerous small plugs containing keratinized epithelium and detritus around the margin. The contents must have fallen out in great part. The surface is covered with epithelial cells, polymorpho-nuclear leucocytes, and keratinized epithelium in a mass of coagulation necrosis.

The stroma varies in different parts, from œdematous young granulation tissue with stellate, epithelioid and giant cells at the surface under the coagulation necrosis, to a very cellular fibrous tissue, with numerous capillaries and spindle-shaped long nuclei deeper down. In places the stroma is homogeneous and stains pink with eosin, like hyaline. There are areas of round cell infiltration in the stroma. The included plugs

and cylinders of epithelium comprise all the epidermis layers arranged in the same order as in the skin—a cylindrical or cuboidal layer next to the stroma, then polyhedral cells of the stratum mucosum showing prickles most distinctly with Van Giesen's stain, then two or three layers of spindle cells with pigment which takes the hæmatoxylin stain—the stratum granulosum. The outermost layer lining or filling the cavity of the plugs or cylinders is of loose keratinized epithelium, sometimes arranged compactly,

Where the centres are cystic we find besides the keratinized epithelial flakes, fat cells, cells which have undergone fatty degeneration, leucocytes and salts, granular and deeply stained with hæmatoxylin. Cell multiplication is very active, as evidenced by the many divided and dividing nuclei; 2 to 5 nuclei are contained in some cells, connected as if budding.

Into the basal layer of these cylinders there may be ingrowths of papillæ, explaining an unusual appearance, namely, a mass of fibres and connective tissue cells cut across in the centre of one of the above described plugs of epithelial cells. In the deepest part of the invading tumor the cylinders become very small, even narrowed to single cells separated by the same cellular stroma. Anastomosis is very free, many branches spreading throughout a loose stroma. The arteries included in the section show marked endarteritis and round cell infiltration of the adventitia also.

In staining the sections the Van Giesen method was found valuable in staining the stroma and the prickle cells. The keratinized cells stain yellow, the young stroma stains dull red. Gram's stain used for keratohyalin by Ernst' shows it well, staining these cells deep blue.

Sections of the pink granulations over the surface of the bone show granulation tissue without evidence of tumor.

The lymph glands of the popliteal space and groin show fatty atrophy and connective tissue formation, thickened capsules and endothelial hyperplasia. There are no metastases.

The popliteal artery and vein with surrounding tissue show no evidence of tumor growth about them. They are united by dense fibrous tissue. There is evidence of endarteritis.

The synovial membrane described as hemorrhagic shows round cell infiltration and vessels filled with blood, which also suffuses the surrounding tissue.

The bone cut across near the knee shows no microscopic evidence of carcinoma; it appears normal.

Section of fragments of bone with tumor and granulations mixed in an irregular friable mass. The tumor alveoli and stroma are as described above. Adjoining whorls are seen to become conglomerate, mixing together their contents of keratinized epithelium and fatty necrotic substances and bounding this by their several epidermis layers. Secondary papillæ project into the primary alveoli, giving a complicated appearance on section. In the proximity of the bone the cellular stroma is strewn with giant cells with centrally massed large oval vesicular nuclei containing big nucleoli. These are osteoclasts, for wherever the bone is seen undergoing absorption it is lacunar in nature and the Howship's lacunæ contain osteoclasts to fit them. The tumor cells do not come in direct contact with the bone, being separated by stroma and osteoclasts.

The bone is very dense, with narrow compact lamellæ containing few corpuscles, and these are small and far apart. The Haversian canals are filled with cellular connective tissue, vessels, old bone fragments looking as if shelled off, and osteoclasts in lacunæ. Branching canaliculi are distinctly seen. There is new formation of bone going on. The new lamellæ are arranged at an angle to the old ones, they take the eosin stain deeper and are lined by osteoblasts, cuboidal and spindle-shaped. There is a granular line stained with hæmatoxylin between old and new bone.

Section of bone with invading tumor at the seat of fracture. The lamellæ are narrow and closely packed and enclose bone corpuscles at rather wide intervals. Some of the corpuscles nearest the invading tumor are enlarged and the cells are deeply stained. The Haversian canals are irregular in contour, of various sizes, and filled with granular detritus and fragments of bone. About their rim there is lacunar absorption, the grooves being small. The bone, where invaded, is being absorbed by the osteoclasts, for in every Howship's lacuna can be seen a giant cell such as Kölliker[8] describes, or large osteoblasts which here take on the function of osteoclasts and are such.

These osteoclasts vary in size and shape, each fitting exactly a groove in the bone hollowed out to fit the absorbing agent. Some of the cells are seen completely surrounded by bone, others have only one-third of their body enclosed by the lacuna. The shape varies from oval, round, oblong, large cells to elongated flat cells lining quite a large part of the bone surface, looking almost as if one of the outer lamellæ had broken off abruptly and taken in many large nuclei. The size varies from an osteoblast to cells five or six times as big.

The nuclei are either massed in the centre or arranged around the periphery; they are large, round or oval, and vesicular. The protoplasm of these osteoclasts is granular and stains deeply with eosin, especially at the centre. The edge of the cell next the bone is rough; the other borders of some cells seem of double contour and quite smooth.

No foreign bodies were detected in any of these bodies next the bone, yet some of the giant cells near by included epithelial debris.

The protoplasm of some osteoclasts is drawn out like a pseudopod and pushes in between the connective tissue cells. Where granulations seem to fill the lacunæ one finds osteoclasts between them and the bone wall.

There is evidence of new bone formation. To the characteristics of newly deposited bone already mentioned can be added the closer approximation of bone cells—there being more of them than in the older adjacent bone. The medullary spaces between the cancelli of bone are filled with newly formed fibrous tissue and granulation tissue containing giant cells and all the cells usually found in embryonal tissue. There are also numerous capillaries and larger vessels in the spaces. The bone cells vary in size and appearance, as do the bone corpuscles, some being round and spindle-shaped, others stellate. They can be best studied in the newly deposited bone or in bone undergoing absorption. It would seem as if when about to be freed from their imprisonment they take on active functions again and are stained more readily.

As in other sections of bone, no tumor cells come in direct contact with the bone. The tumor advances as described above. There are small fragments of bone in the granulations, which look as if they had been eaten off and left. There is a deposit of new bone in the vicinity of the tumor and evidence of absorption going on in the same microscopic field.

CASE II.—W. J. R., white, æt. 54, admitted June 26, '95.

For 49 years the patient has had discharging sinuses in the thigh communicating with necrotic bone.

Operation, June 28th, by Dr. Bloodgood. Amputation of thigh at the upper third. Notes made at the operation refer to the great friability of the bone, the thickened periosteum, thin shaft and presence of a sequestrum.

Nov. '96. Patient reports himself well.

The pathological report is as follows: The diseased condition of the bone begins 26 cm. above the condyles and involves the shaft for 16 cm. The last piece of bone removed, 3 cm. below the trochanter, appears healthy. The periosteum is thickened, the shaft, stripped of periosteum, is rough and presents minute spicules. The shaft varies in thickness from 3 to 6 mm., and there is very little cancellous bone. It is brittle, fracturing easily. The medulla above seat of disease contains much fat and oily material. At the seat of disease there is no involucrum. In the sinus leading from the diseased bone there is a sequestrum 6 cm. long and 1½ cm. wide. The periosteum about the necrotic portion is 5 to 6 mm. thick, and on section is pearly white and appears striated at right angles to the long axis of the bone. On the surface next to the shaft it is covered with a yellow necrotic friable tissue covering a leathery surface. Fine spicules of bone are imbedded in this. The odor is foul. The surface of the shaft is rough and hard. The medullary cavity is filled with hard bone mixed with thick leathery tissue, and is riddled with small cavities containing the same material as covers the shaft. The only attempt at new bone formation is in the medullary cavity. No attempt at formation of healthy granulations is evident. About the area of disease the shaft exhibits exostoses 1 to 1½ cm. in length. The knee joint is normal in appearance.

Microscopical examination of the tissue between the periosteum and bone described as striated and friable with necrotic border next to the shaft, shows it to be made up in the main of large swollen polygonal cells with oval vesicular nuclei. The arrangement is such as one sees in the stratum mucosum of the skin. There are papillæ projecting into the mass from the periosteum, which is thickened and infiltrated with small round cells. The cells next the papillæ are prickle cells; those nearer the shaft do not show the prickles. The cells are massed in varying density. According to the location of the papillæ we get lighter and darker stained masses, the darker being more compact and approaching the cancroid pearl in appearance, but there is no cornified nor degenerated centre. Toward the bone the cells are flat and the nuclei lose the ability to stain. A thin layer of cornification covers their surface. Many of the nuclei are vacuolated. The papillæ are very cellular. There is an absence of the stratum granulosum and lucidum; simply a uniform growth of the mucosum and corneum. There is considerable endo- and periarteritis. The muscle and connective tissue show no tumor invasion. The leathery material described in the medulla is like that just described.

Examination of the cortical bone from the shaft shows no tumor growth into it. The dense bone presents a feathery appearance commonly seen in eburnated bone. The edges show lacunar absorption.

A number of cases of squamous epithelioma developing in sinuses and old scars which would come under the grouping I have purposely omitted, since the pathological description of the tumor is in every case essentially the same as in Case I. Two of the cases might be considered carcinoma developing in osteomyelitic sinuses, but the history does not fully substantiate this. In these cases the sinuses were lined by the tubules and plugs of epithelial cells continuous with the tumor mass in the bone itself. The invasion of the bone resembled that described in Case I.

The cases reported bring to mind several most interesting subjects in pathological histology: the development of carcinoma in sinuses, scars and ulcers, its invasion of bone, the peculiar character of epithelial growth, and the bone formation and absorption due to the invading tumor. They are interesting especially because they show side by side the picture of a typical squamous epithelioma and a mere enormous hyperplasia of the epithelial elements of the stratum mucosum in bone. The one is evidently quite malignant; the other does not appear to be very destructive in its growth, but merely a filling in of the space made void by the osteomyelitic process. The two tumors have their homologues in the epithelial growths in sinuses, ulcers and scars, some being typical epitheliomata, others simply hyperplastic growths of epithelium lining the sinus walls.

There is this point to be noted in Case II differing from any yet described—the great development of the cells of the stratum mucosum to the exclusion of the granulosum and lucidum. There is simply a single layer of cuboidal cells covering the papillæ, then 10 to 15 layers of large swollen polygonal cells covered by a thin layer of cornified epithelium. This not only fills the sinus and medullary cavity, but pushes in between the periosteum and the shaft, nowhere penetrating the bone itself. It may be compared in a way with a case of great epithelial cell hyperplasia of the outermost layers of the epidermis described by Busch[16] in a case of lupus. Here there was an epithelial papillary growth covered by thickened, horny epithelium spread over the surface, finally breaking into the connective tissue and forming carcinoma.

Typical squamous epitheliomata in scars, ulcers and sinuses are not uncommon. There are only twenty-eight cases reported in which the epithelioma developed in the sinus following osteomyelitis. From the histories of many cases of epithelioma in ulcers I infer that a few if more accurately described would come under the heading of carcinoma in sinuses following osteomyelitis. Some give a history of osteomyelitis. See Van Hook,[1] Schindler,[2] Boegehold.[4] Borchers[3] in 1891 collected all the cases up to his time, numbering twenty-five. He records cases of König, Dittrich,[10] Nicoladoni,[11] Esmarch,[13] Fischer,[12] Bartens, Cornil and Ranvier,[6]

Winiwarter,[14] Hannover[16] and Volkmann.[18] Another case is recorded by Feigel.[5] One of Van Hook's[1] two cases was undoubtedly carcinoma developed in an old fistula communicating with necrotic bone. Von Friedlander's[17] three cases, reported in 1894, are the last recorded. All of the cases described have many points in common with our first case.

Clinically, the development of the disease in those beyond 40 years of age, the common involvement of the lower extremities, the uncertainty of fixing the exact time of development, its slow growth, the foul odor, the long existence of the fistulæ, the absence of pain until the carcinoma begins to develop, the ease with which the bone is broken, the fixation of the neighboring joints and ankylosis of adjoining bones, the infrequent involvement of lymphatic glands or other organs, and its almost sure recurrence unless the limb be amputated, are all most noteworthy points.

Volkmann[18] says that recurrence occurs in a few weeks or months after the operation, if at all; if not within 1 to 1½ years, it seldom occurs.

The pathological picture is not to be confused with any known disease of bone or sinus. The crater-like ulcer or cauliflower excrescences made up of individual oval yellowish white masses, are enough to make the diagnosis. Finding the same papillary growths in the medullary cavity is not calculated to make one think of simple osteomyelitis. The bone next the tumor is either soft and spongy or denser than normal bone. It is increased in circumference and the medullary canal may be smaller than normal. Osteophytes may form on the surface and the bone may rarely present the appearance of spina ventosa. Fracture is common.

The microscopical picture is that of squamous epithelioma modified in appearance according to the amount of degeneration and bone absorption and the greater or less development of tubules, alveoli or cysts. The tumor cells nowhere come in direct contact with the bone, being separated by connective tissue and giant cells or osteoblasts. The thickness of the growth varies, but it is thickest in the cloaca, and in places looking like granulation tissue. The sequestra in Nicoladoni's[11] cases were not invaded by epithelial cells.

Borchers[3] refers to the advance of the tumor into the Haversian canals. Our cases do not substantiate this, the epithelial cells never being found separate from the main growth.

In none of the cases were metastases found in the internal organs and rarely even in the lymph glands. The swollen glands usually became of normal size after amputation of the limb. The reason of the infrequent metastases is found in the sclerosis and condensation of tissues about the tumor and its very slow growth.

Thinking of the etiology and histogenesis of the tumors, one would naturally class those described with tumors developing in ulcers, fistulæ and old scars. Many theories have been advanced to explain them: Virchow's[19] idea of chronic irritation, mechanical and chemical, being most naturally first alluded to. The question whether the connective tissue growth or epithelial proliferation be the primary factor has been most actively debated since Ribbert[9] so strongly advocated the former view. Boegehold,[4] who reported several cases like my first one, believes in their connective tissue origin, and says that the epithelium is lost over scars and ulcers. He says: "If the surface epithelium cannot cover over the granulation surface, one cannot see why it shall grow into the depths of the granulation tissue."

Langenbeck,[20] in discussing the development of carcinoma in lupus, expresses the view that the cause of development is like that in traumatic scars, a continuous irritation and the carcinoma develops from remaining epithelial cells. It is distinct from the lupus growth. "It is difficult to reconcile the notion of lupus—a granulation tissue—passing directly into carcinoma, because of our view that epithelioma must come from pre-existing epithelial cells."

Wenk,[21] who believes in this direct transition, concedes that the epidermis projections have not been entirely destroyed. Langenbeck[20] attributes its formation to development of epithelium in the outlying scar. Schindler[2] cites cases to prove the development from the scars—either from the covering epithelium or glandular organs of the skin left intact by the lupus process. He answers Boegehold's[4] argument cited above, by explaining that the surface epithelium is prevented from spreading superficially by continual irritation (pressure or secretion) and therefore it dips down deeply where not exposed to these influences. Hulke,[22] in describing two cases of carcinoma in old scars, ascribes them to purely local causes. Pedraglia[23] refers to old age and periodic irritation as predisposing causes. This view that old age influences the growth corresponds with that of Verneuil referred to by Marcuse:[24] "Ein locus minoris resistentiae" of the connective tissues, the epithelium retaining and increasing its activity. Marcuse uses this theory in explaining the growths in the granulations covering ulcers—the granulation tissue, when not going on to scar formation, being not so resistant to epithelial hyperplasia as normal tissues. Here the epithelium grows into the tissues as stated by Thiersch[25] in his most valuable contribution to the etiology of epithelioma of the skin.

It is not much disputed now that epithelium only forms from preformed epithelium and not from leucocytes or connective tissue cells. This materially aids the histogenetic study of these tumors. Whatever the cause, the practical lessons obtained from them are of much value to the surgeon, and one is not tempted to use tentative measures to stop a growth which he knows by experience and microscopical study to go steadily onward in its course until it is excised radically.

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10. Dittrich: Prager Vierteljahresschrift, 1847, II.

11. Nicoladoni: Arch. f. klin. Chir., No. 26, 1881.

12. Esmarch: Langenbeck's Arch., XXII.

13. Fischer, S.: Zeitschr. f. Chir., 1881.

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17. v. Friedlander: Beitrag zur Kenntniss der Carcinomentwickelung in Sequesterhöhlen und Fisteln. Deutsche Zeitschr. f. Chir., 1894.

18. Busch: Langenbeck's Archiv, XV, p. 48.

19. Virchow: Die krankhaften Geschwülste, Bd. II, p. 487.

20. Langenbeck: Berlin. klin. Wochenschr., 1879, p. 329.

21. Wenk, L. H.: De exemplis nonnullis carcinomatis epithelialis exorti in cicatrice post lupum exedentem relicto. Kiel, 1867. Reference from Schindler, see above.

22. Hulke, J. W.: London Medical Times, Vol. 1, 1873, p. 135.

23. Pedraglia: Vier Fälle von Epithelialkrebs auf alten Narben. Giessen, 1853.

24. Marcuse, J.: Deutsche Zeitschr. f. Chirurgie, Bd. VII, p. 550.

25. Thiersch: Der Epithelialkrebs, namentlich der Haut. Leipzig, 1865.

ON THE BLOOD-PRESSURE-RAISING CONSTITUENT OF THE SUPRARENAL CAPSULE.*

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Both clinical experience and laboratory research have shown that the suprarenal capsule is an organ of vital importance.

Physiologists† have proved that a very small quantity of an aqueous extract of the medullary substance raises the blood pressure to a great height above the normal. It has also unequaled power in reviving a poisoned heart. Gottlieb,‡ for example, has shown that it will revive the heart of a rabbit which has practically stopped beating in consequence of an intravenous injection of chloral hydrate.

Bates§ applied an aqueous solution to the eye and found that it exerted a marked vaso-constricting action. In numerous cases of congestion a small quantity dropped into the conjunctival sac brought about an immediate pallor, lasting for some time. According to this writer the extract is very useful in prolonged operations, for, when repeatedly applied, hæmorrhage is prevented and cocaine anæsthesia is in consequence indefinitely prolonged. As the result of his two years' use of the extract Bates concludes "that within the limits of its sphere of activity there is absolutely no other substance which can take its place."

Other experiments‖ go to show that the aqueous extract is a powerful poison when injected directly into the circulation and may lead to fatal results.

The various extracts that have been used in these experiments were mixtures of unknown substances, and it is as yet an unsolved question whether the various actions at present ascribed to the gland are due to one and the same substance.

We are at present interested in the isolation of the blood-pressure-raising constituent, for in a purified state, separated from all other constituents, it might become a therapeutic agent of great importance.

On the chemical side but little advance has been made over Vulpian's* striking original contribution more than forty years ago. Vulpian observed that the juice expressed from the suprarenal capsule of many different animals behaved in a striking manner toward ferric chloride and toward solutions of iodine, giving with the former reagent an emerald green color, and with the latter a beautiful rose carmine tint. No other tissue of the body, so far as investigated by Vulpian, gave these reactions.

Virchow† substantiated Vulpian's statements, but added nothing new. A year after Vulpian's first announcement his second paper appeared in conjunction with Cloëz,‡ verifying and extending his first observations and stating his failure to isolate the chromogenic substance or substances to which the above reactions are due.

Equally unsuccessful were Arnold§ and Holm.‖ Kruken-

* Read before the Association of American Physicians, May 6, 1897.

† Schäfer and Oliver, Journal of Physiology, xvi (1894) and xvii (1895); Szymonowicz and Cybulski, Wien. med. Wochenschrift, 1896, No. 6.

‡ Arch. f. exp. Pathol. u. Pharmakol., xxxviii, 106.

§ New York Medical Journal, lxiii (1896), 647.

‖ Foa and Pellacani, cited in Maly's Jahresb. d. Thier-Chemie, xiii, 129; Marino-Zuco, ibid., xviii, 231; Gourfein, Rev. Méd. de la Suisse Romande, Oct. 20, 1895; Compt. rend., cxxi (1895), 311–314.

* Note sur quelques reactions propres à la substance des capsules surrénales, Compt. rend., xliii (1856), 663–665.

† Virchow's Archiv, xii (1857), 481–483.

‡ Compt. rend., xlv (1857), 340–343.

§ Virchow's Archiv, xxxv (1866), 64–107.

‖ Journ. f. prakt. Chemie, c (1867), 150.

berg,* years after, repeated the work of Arnold and came to the conclusion that the chromogen of the suprarenal capsule is a non-volatile, nitrogenous and ferruginous organic acid which is probably related to the turacin of the musophagidæ and to chlorophyll. He assumed that the substance giving the green color with ferric chloride is not the chromogenic substance of Vulpian, but more likely pyrocatechin accompanying the chromogen. Attention being thus attracted to the possible occurrence of pyrocatechin in the suprarenal capsule, others took up the subject.

Brunner† found that an alcoholic extract can be made to give nearly all of the reactions of pyrocatechin; thus, it gives the well-known green color with ferric chloride, passing into a fine red on the addition of ammonium tartrate and a few drops of an alkali; it reduces silver nitrate at room temperature, and Fehling's solution on boiling. The addition of an alkali soon causes it to take on a dark brown color, lead acetate gives a precipitate, sodium nitroprusside and very dilute ammonia give a wine-red color. All of the above reactions being given also by pyrocatechin, Brunner concluded that Krukenberg was right in his belief that pyrocatechin is present in the suprarenal gland.

After the discovery of the blood-pressure-raising property of the suprarenal gland, B. Moore,‡ working in Schäfer's laboratory, came to the conclusion that Vulpian's chromogen and the blood-pressure-raising constituent are identical. He based his opinion on the fact that chemical operations which destroy the color reactions by oxidizing the reducing agent appear also to destroy the blood-pressure-raising constituent. That the solubilities of the active principle are the same as those of the reducing agent appears also to support this opinion.

Fraenkel§ worked with residues obtained with the help of alcohol and acetone as solvents. These residues raise the blood pressure and do not contain pyrocatechin, and on the strength of the ferric chloride reaction and its reducing power he concludes that the essential principle of the residue is a nitrogenous derivative of the *ortho*dihydroxy-benzene series.

According to Fraenkel both Krukenberg and Brunner are wrong in their opinion that the suprarenal gland contains pyrocatechin. Fraenkel concludes, like Moore, that the blood-pressure-raising constituent and Vulpian's chromogen are one and the same substance.

More recently still, Mühlmann‖ has attempted to prove that the blood-pressure-raising constituent is a pyrocatechin derivative. He asserts that on boiling fresh suprarenal capsules with dilute hydrochloric acid the active principle is decomposed and the pyrocatechin which is split off may be taken up with ether. Mühlmann has not, however, furnished conclusive chemical proofs for his assertion. Both Mühlmann and Brunner might have settled this point by precipitating the supposed pyrocatechin with lead acetate and analyzing the lead salt thus obtained. Pyrocatechin may be present in small amounts in the gland, but no proof of this has yet been furnished.

There is therefore at present great diversity of opinion as to the chemical character of the blood-pressure-raising constituent of the gland.

Whatever the probability may be of the correctness of this or that view, it is to be noted that all of the above-named investigators have based their conclusions on reactions made with aqueous, alcoholic or acetonic extracts; none of them have even roughly isolated a definite chemical compound. The subject is one of great difficulty, and our own work is at present merely preliminary, but we have arrived at the following conclusions which we believe to be borne out by our experiments.

First, we have found by isolating the blood-pressure-raising constituent in the form of a benzoyl compound and decomposing it, that the active principle is a substance with basic characteristics and that it must in all probability be classed with the pyrrol compounds or with the pyridine bases or alkaloids.

Second, that pyrocatechin cannot be split off from the isolated active compound by boiling with acids, as has been asserted.

Third, we have found that a carmine-red pigment can be separated from the sulphate of the active principle without destroying its power to raise the blood pressure.

Fourth, in addition to this, we have isolated from the crude benzoyl product a volatile basic body which fumes in the air and which emits an odor very much like that of coniine.

Method of Isolating the Active Principle in the Form of a Benzoyl Compound.

We have used sheep's glands in large quantity. The medullary substance of the fresh glands was scraped out, dried on the water-bath at 60° C., ground up finely, and extracted with ether for several days until the fats and the substance known as Manasse's jecorin were removed. In this way a fine dry powder of a grayish white appearance is obtained, the aqueous extract of which is very active in raising the blood pressure.

With 100 grammes or more of this powder, representing one kg. in weight or about 1000 fresh glands, we proceeded as follows: The powder is repeatedly extracted with warm water acidulated with a few drops of dilute sulphuric acid until the gland has yielded up all of its chromogenic substances, as tested by Vulpian's reactions. This aqueous extract is evaporated on the water-bath to a small bulk, a large excess of strong alcohol is then added and the whole allowed to stand 24 hours, by which time the proteids have all settled out. The alcoholic fluid is then filtered and the greater part of the alcohol removed by distillation; the remainder is driven off on the water-bath. The entire removal of the alcohol is necessary, and in order to avoid too great concentration of the acid fluid, which seems to destroy some of the active principle, water has now and then to be added. The brownish fluid when filtered gives all the well-known reactions characteristic of Vulpian's chromogen, and on neutralizing the sulphuric acid we found the filtrate to be physiologically very active.

* Virchow's Archiv, ci (1885), 542–591.
† Schweizer. Wochenschr. f. Pharmacie, xxx (1892), 121–123.
‡ Journal of Physiology, xvii (1895), Proc. Physiol. Soc., p. xiv.
§ Wiener med. Blätter, 1896, No. 14–16.
‖ Deutsche med. Wochenschr., 1896, No. 26, 409–411.

This filtered fluid is next treated with the proper quantity of benzoyl chloride and sodium hydrate according to the Baumann–Schotten method of forming a benzoyl compound. There results a tarry substance of a light yellow color which sticks to the sides of the separator funnel and which is collected and washed until the wash fluid no longer gives an alkaline reaction. It is next dissolved as far as possible in alcohol and the alcohol evaporated. The residue is then treated with ether, which takes up the greater part of it, the ethereal solution is filtered and the ether driven off.

The residue, which is of tarry consistence and amber color, is taken up in strong alcohol from which all basic substances have been removed by distilling from tartaric acid. It is then boiled for two hours with animal charcoal previously well washed with purified alcohol. After filtration and the evaporation of the alcohol a considerable quantity of crystalline residue is obtained which is found to consist of the benzoyl compound of the active principle contaminated with other benzoyl derivatives and which we may call the crude benzoyl product. It is insoluble in water, alkalies or acids of ordinary strength, is soluble in alcohol, ether, glacial acetic acid and concentrated sulphuric acid.

It is of interest in this connection to note that benzoyl chloride effects the complete removal of the blood-pressure-raising constituent from an aqueous solution. This is proved by the fact that the filtrate from the insoluble benzoate no longer gives the characteristic chemical reactions of the active principle, and that chemical manipulations no longer yield a blood-pressure-raising constituent. Indeed, an injection of a sufficient amount of the material left after the sodium benzoate and the excess of alkali have been removed, causes a sharp and sudden fall of pressure instead of a rise.

It was not until long after we had made use of benzoyl chloride as a precipitant of the active principle that we obtained access to Fraenkel's* paper. From it we learned that a syrupy substance is thrown out when benzoyl chloride is shaken up with a pyridine solution of an extract of the gland. Fraenkel did not succeed in crystallizing this benzoyl compound, nor did he attempt to decompose it in order to ascertain whether it was in reality a benzoate of the blood-pressure-raising principle.

METHODS OF DECOMPOSING THE BENZOYL COMPOUND.

A quick method always used by us as a qualitative test is as follows: The compound is dissolved in as little concentrated sulphuric acid as possible, crushed ice is slowly added, and the benzoic acid which has been split off is shaken out with ether. On neutralizing the solution we found it to give the reactions characteristic of aqueous solutions of the medullary substance. We have not considered this method adapted to the decomposition of large quantities of the product.

Decomposition of this benzoyl product was effected by means of an alcoholic solution of sodium alcoholate, and also with strong hydrochloric acid and alcohol, but these methods were found to be less satisfactory in practice than the following, which is the method on which we now rely. The benzoyl compound is dissolved in glacial acetic acid, the solution heated to near the boiling point, and an equal volume of a 25 per cent. solution of sulphuric acid actively boiling is slowly poured into the hot acetic acid solution, the whole being shaken meanwhile. The flask is now attached to a back-flow condenser and heated on a small flame for about ten minutes.

The solution is next diluted with water and allowed to cool, the benzoic acid, which has been thrown out, is filtered off and the rest is removed with the help of ether.

Mixed with the benzoic acid which has been removed by filtration is found a dark brittle substance which softens on the water-bath, and which we assume to be a benzoyl compound of unknown composition which was apparently unaffected by the dilute sulphuric acid. On dissolving it in concentrated sulphuric acid and diluting with crushed ice, the resulting fluid gives none of the reactions characteristic of suprarenal extracts.

After decomposing the benzoyl product with hot dilute sulphuric acid and removing the benzoic acid thus split off, we next get rid of the acetic acid by repeated partial evaporations, taking care not to let the solution become too concentrated and thus perhaps injure the active principle. After the removal of the acetic acid the sulphuric acid is precipitated with the help of lead carbonate. The lead sulphate is removed and the filtrate is allowed to stand *in vacuo* over sulphuric acid until it has become of tarry consistency. It is then exhausted with ether, acetone and absolute alcohol in succession.

The residue is physiologically very active, and it gives all the reactions characteristic of an aqueous solution of the gland—a beautiful rose color on the addition of an alkali, a green color with ferric chloride, reducing silver nitrate, etc.

However, we are not yet dealing with a pure substance. If we neutralize an aqueous solution of the product thus obtained with a free alkali or with a carbonate of the alkalies, an overpowering odor much like that of coniine is perceived. As this odor passes that of pyridine seems to take its place. The basic substance thus liberated fumes in the air or when a glass rod moistened with hydrochloric acid is brought into its neighborhood. To remove this basic substance we made an aqueous solution of the active principle as above isolated, rendered it faintly alkaline with sodium carbonate and shook out with ether several times in succession. But this method does not remove all of the coniine-like substance. To effect this we were obliged to make the active principle strongly alkaline with sodium hydrate before shaking out with ether. The aqueous solution, in consequence of the addition of the free alkali, takes on a deep red color, and carmine red flocks are thrown out. After the removal of the coniine-like substance with ether, the fluid containing the red flocks was acidulated with sulphuric acid and the carmine-red substance was filtered off. The clear filtrate, which was a pale straw color, was concentrated *in vacuo*, and the active principle taken up in weak alcohol. On account of the insolubility of the sulphate of the active principle in absolute alcohol it is difficult to obtain this entirely free of sodium sulphate. We hope in future to remove both the coniine like substance and the pigment with the help of ammonia. The presence of pyridine in our ammonia prevented our using it for this purpose.

* Wien. med. Blätter, 1896, No. 14–16.

This volatile base of a coniine-like odor has not hitherto been described as a constituent of the suprarenal capsule. The beautiful carmine-red pigment we take to be identical with the red substance which many other observers have found to be thrown out as a precipitate when ammonia is added to a concentrated aqueous solution of the gland, or when a solution is evaporated in the presence of lead acetate.* Others have believed this red precipitate to be the oxidation product of the active principle of the gland, but we shall presently see that the active principle is still present in the filtrate from the carmine-red body. We have as yet made no experiments with this pigment except to note that it is but slightly soluble in dilute alkalies and insoluble in dilute acids, and that iodine destroys the color. Our method appears to make the further study of this substance possible.

The coniine-like substance we have secured in the form of its hydrochlorate, and with it we have made certain studies which will be published at a later date.

Characteristics of the Blood-Pressure-Raising Constituent as obtained by decomposing its Benzoyl Compound.

We have now obtained the active principle in the form of a sulphate. As thus far isolated it is a hygroscopic, straw-colored residue which tends to crystallize on standing over sulphuric acid, agglomerates of small crystals forming on the edge of the bowl and the entire residue taking on a semi-crystalline appearance. This sulphate does not contain the volatile coniine-like substance, nor do we find the carmine-red pigment which falls out on the addition of an alkali. Alkalies no longer liberate the coniine-like substance, nor do they throw out the red pigment, but they cause a brownish discoloration, and on heating, alkaline vapors, probably ammonia, are given off.

Our sulphate is very active physiologically. A small quantity suffices to raise the blood-pressure as seen in Fig. 1, and it is therefore evident that we have isolated the active principle but slightly contaminated with other substances.

A final product even more active in small quantities is that whose action is shown in Fig. 2, where the mercury is driven out of the manometer. This more active compound still contains much of the coniine-like substance, and at once throws out the carmine-red pigment on the addition of alkalies. The sulphate of the coniine-like substance does not, as we have seen, raise the blood pressure; it therefore remains for us to consider whether the carmine-red substance which is precipitated on the addition of alkalies, either alone or in conjunction with small quantities of oxidizing agents, has any physiological significance or stands in any chemical relation to the blood-pressure-raising constituent. We incline to the opinion that this substance, which in the original aqueous solution of the gland gives with iodine water the "teinte rose-carmin tout à fait remarquable" of Vulpian, is in nowise connected with the blood-pressure-raising constituent. We have repeatedly removed or destroyed this substance by boiling solutions containing it with strong ammonia or with sodium hydrate, and have always been able to separate subsequently an active material. In proof of this we append Fig. 3, showing a great rise of blood pressure, although the material from which this active principle was obtained had been boiled for one hour with a 5 per cent. solution of sodium hydrate. After such treatment with alkalies, care must be taken in the subsequent evaporation of the alcohol with which the active principle is removed, to keep an acid reaction, as otherwise the greater part, if not all of it, will be destroyed by oxidation. And unless all evaporations are carried on under reduced pressure, much material will be lost, even with the above precaution.

Although somewhat contaminated with its own decomposition products, this final sulphate has all the characteristics of an active substance. As shown by repeated experiments, it promptly raises the blood pressure, it constricts the vessels of an inflamed eye, and when injected into the dorsal lymph sac of the frog it acts like a narcotic or cerebro-spinal poison.

As freed of the red substance the sulphate of the active principle behaves as follows: It is very soluble in water, fairly soluble in weak alcohol (50 per cent.), almost insoluble in absolute alcohol, and quite insoluble in ether, acetone, ligroine and chloroform. Its aqueous solution, even when freed from adherent sulphuric acid, has a slightly acid reaction. The addition of iodine water to a neutral solution does not give a rose-red color. Alkalies added to a strong solution give a brown color which deepens on heating. Ferric chloride gives a purplish brown, almost black in concentrated solution, which on the addition of tartaric acid and an alkali passes into a deep red color. Before the removal of the carmine-red substance the addition of ferric chloride gives the well-known emerald green color, which passes into red on the addition of an alkali.

It is evident that our sulphate gives Vulpian's ferric chloride reaction, though somewhat changed by the removal of what we take to be the chromogenic substance which gave his iodine reaction. It also promptly reduces silver nitrate in alkaline solution, but does not reduce Fehling's solution even on boiling.

Probable Relation to the Alkaloids.

More than a year ago, during our first studies with suprarenal extract, we were struck with the fact that every extract entirely free of proteids and physiologically active gave a fine pyrrol reaction when subjected to dry distillation. This is evidenced both by the odor and by the pine sliver reaction. A small quantity of the isolated sulphate also gives the pyrrol reaction when heated either alone or with zinc dust.

We attach considerable importance to this reaction. As is well known, alkaloids in general give pyrrol on dry distillation; morphine, for instance, on being heated with 10 parts of zinc dust gives off pyrrol, ammonia, trimethylamine, pyridine, phenanthrene, etc.* During the past winter we made

* Holm, Journ. f. prakt. Chemie, c (1867), 150.

* We are well aware that certain salts of glutaminic, pyromucic and its related acids also yield pyrrol on dry distillation. These compounds, however, like the proteids and their allies, appear to us to be excluded.

several attempts to prove the presence of pyridine among the products of dry distillation of the active principle as above isolated, as its detection would prove that our principle was to be classed among the alkaloids.

In attempting to show the presence of pyridine we heated the active principle with zinc dust in a current of dry hydrogen and passed the distillation products through a test tube and two small flasks, the tube being placed in a cooling mixture, the first flask being partly filled with dilute sodium hydrate, and the second with dilute hydrochloric acid.

At the close of the experiment the test tube gave off alkaline vapors that smelled strongly of trimethylamine and had in addition a peculiar sweetish odor. The contents of the test tube diluted with water gave a precipitate with bromine water and with copper sulphate, but with the latter reagent the fine blue color characteristic of pyridine did not appear. The presence of amines seems to render difficult the detection of small quantities of pyridine. The contents of the third flask on exposure to the air took on a rose-red color and after a time threw out a precipitate of the same tint. Both flasks gave off the odor of benzaldehyde.

The following experiment was also made with a little of the sulphate, which no longer gave the rose-red reaction with iodine but which still contained a little of the coniine-like substance. For two hours it was kept at 150° C. in a sealed tube with 25 per cent. hydrochloric acid. On shaking out with ether a considerable crystalline residue was obtained which, without much purification, melted sharply at 120° C. and had all the properties of benzoic acid.

In the above decomposition experiments the quantity of material at command was small, perhaps not more than one-fifth of a gramme at a time, and not entirely pure. We do not, therefore, lay much stress on our failure to detect pyridine.

The fact that the nitrogen of our compound is given off in the form of amines and pyrrol gives strong ground to believe that our substance is to be classed with the pyridine bases, using this term in a broad way. Its basic character, its ability to take up acid radicles, as illustrated by the formation of a benzoyl product, its reducing power and its color reaction with ferric chloride are all points which can be urged in support of this view. Furthermore, cupric acetate, the serviceableness of which as a precipitant of carbo-pyridine bases has been shown by Gautier and Landi,* also precipitates our active principle; and iodine chloride, which Dittmar† found to give brown or yellow halogen addition-derivatives with a large number of the alkaloids, gives with a neutral or slightly acid solution of our active sulphate a brownish flocculent precipitate.

Of less weight in this connection, but nevertheless of some value, is the fact that its physiological action and its power in small doses is again in accord with what is known of alkaloids. Strychnine, thebaine and other alkaloids are readily called to mind as able to raise the blood pressure, and recently Tunnicliffe‡ has placed piperidine in the same list. The pyrrol* bases are also physiologically active, although less attention has been paid to them.

*Compt. rend., cxiv (1892), 1154–1159.
†Berichte d. deutsch. chem. Gesellsch., xviii, 1612.
‡Centralbl. f. Physiol., x, No. 25, 777.

PYROCATECHIN CANNOT BE SPLIT OFF FROM THE BLOOD-PRESSURE-RAISING CONSTITUENT.

As already said, Mühlmann has stated with great positiveness that the blood-pressure-raising constituent is pyrocatechin joined to some other substance, probably an acid. Mühlmann does not offer sufficient proof for his conclusion; and even had he proved the presence of pyrocatechin in the gland itself, this is a very different thing from showing that it enters into the chemical constitution of the blood-pressure-raising constituent.

We have repeated Mühlmann's work and have found that after boiling the medullary substance with hydrochloric acid, the ether takes up a trace of Vulpian's substance, as well as a substance that reduces Fehling's solution.

The ether residue also gives a precipitate with neutral lead acetate which, on decomposition with dilute sulphuric acid, sets free a compound that gives with ferric chloride the reaction so characteristic of pyrocatechin. Our blood-pressure-raising constituent is not precipitated by lead acetate and could not, therefore, have been responsible for this result.

Furthermore, on decomposing a fairly large quantity of the crude benzoyl product before referred to and shaking out the resulting benzoic acid with ether, we have twice found that the ether has taken up in addition to the benzoic acid a small quantity of a substance which reduces Fehling's solution and gives a precipitate with neutral lead acetate. On decomposing the resulting lead compound with dilute sulphuric acid and neutralizing the filtrate, we obtained a solution which behaved with ferric chloride in the way characteristic of pyrocatechin. The quantity of this lead compound obtained has been too small for analytical purposes.

We consider it, therefore, still uncertain whether or not a little pyrocatechin is present in the gland.

That the blood-pressure-raising constituent is, however, not a pyrocatechin derivative seems to us certain. To prove this we used, not the entire gland nor the medullary substance, but the active principle itself, as isolated by us by decomposing the benzoyl compound.

We have used large quantities of material representing in each experiment the active principle of several thousand glands. We have boiled this with hydrochloric acid of varying strength and for varying lengths of time, and in no case have we been able to find in the ether used as a solvent any trace of a substance that would reduce Fehling's solution or give a precipitate with lead acetate. Inasmuch as some of the chromogenic substance always passes into the ether from acid solutions, these two reactions are both necessary to establish the presence of pyrocatechin. In other words, we have failed to split off pyrocatechin from the active principle as isolated by us. If present, it could hardly have eluded our search, for even a minute quantity may be made to give a precipitate with neutral lead acetate.

*Jac. Ginzberg, Ueber das Verhalten des Pyrrols, etc., Inaug. Diss., Königsberg, 1890.

We propose during the coming autumn to continue this work. Having made arrangements for the use of a large amount of material, we hope to secure both the benzoate and the sulphate in a form pure enough for analysis and for further chemical study.

Summary.

We may summarize the results of our work as follows:

The blood-pressure-raising constituent of the suprarenal capsule may be completely precipitated from an aqueous extract by treatment with benzoyl chloride and sodium hydrate, according to the Schotten-Baumann method.

On decomposing the resulting benzoyl products, a residue is obtained which possesses great physiological activity. It gives the color reactions of Vulpian, reduces silver nitrate and possesses the other specific qualities of suprarenal extracts.

With the help of alkalies a carmine-red pigment may also be separated from these decomposition products. We take this pigment to be that one of the chromogenic substances of Vulpian which gives the rose-carmine color when suprarenal extracts are treated with oxidizing agents or alkalies.

A volatile, basic substance of a coniine-like odor is always found to accompany the crude benzoate. When these substances are removed the active principle is left as a highly active sulphate or hydrochlorate, as the case may be. It is therefore a basic substance. Its salts give a color reaction with ferric chloride; they also reduce silver nitrate, but not Fehling's solution.

It is not possible to split off pyrocatechin from this isolated active principle. The fact that dry distillation causes the appearance of amines and pyrrol in abundance, taken in connection with its ability to take up acid radicles, its reducing power, its precipitability by cupric acetate and iodine chloride, and its physiological action, lead us to conclude that our active principle is to be classed with the pyridine bases or alkaloids.

Addendum, June 15, 1897.

Since the foregoing paper was read before the Association of American Physicians on May 6, 1897, B. Moore has published a paper in the *Journal of Physiology*, vol. xxi, Nos. 4 and 5, May 12, 1897, entitled, "On the Chromogen and on the active Physiological Substance of the Suprarenal Gland." In this paper it is suggested that the active principle may be a pyridine derivative. Moore's conjecture is based, first, on a formula calculated by him from a combustion analysis of Krukenberg, made with an impure, hygroscopic, non-crystalline residue obtained by merely decomposing and drying a precipitate secured out of an alcoholic extract of the gland with the help of basic lead acetate. The calculated formula, the carbon content of which differs by 1.33 per cent. from that actually found by Krukenberg, is $C_5H_{14}NO_4$, and Moore points out that in it the ratio in which the elements carbon and nitrogen stand to each other is the same as in pyridine, C_5H_5N. Now such a calculation, though suggestive to the investigator, furnishes no proof of the presence of pyridine, for Krukenberg could not possibly have had in hand a chemical individual uncontaminated with other constituents of the gland. Krukenberg himself admits that his material was a mixture of unaltered pigment and its decomposition products. It is also certain that it was contaminated with other constituents of the gland. This is proved by the fact that basic lead acetate precipitates several of the constituents of the gland which pass into alcohol, and also by the fact that the analysed material contained 0.068 per cent. of sulphur and from 1.18 per cent. to 1.44 per cent. of ash.

A second reason given by Moore in support of his conjecture is that when "some suprarenal extract was cautiously fused with caustic potash so as to avoid charring, the peculiar odor of pyridine was at once obtained." He admits that proteids were present in this extract, and that pyridine and its homologues are formed in the destructive distillation of proteids, but states that the experiment was "conducted so as to avoid charring," and considers this a sufficient safeguard. This experiment has also no value, for the odor of pyridine can always be obtained when a mixture of dry, powdered proteid and powdered caustic potash are fused together so as to avoid charring. This experiment, therefore, must be made with material entirely free of proteids. Since reading Moore's paper we have fused a little of our active principle with caustic potash, but have failed to detect pyridine. If present in the molecule of the active principle, it is evident that larger quantities of the material must be used to prove it. Only indisputable chemical proofs can establish the presence of pyridine; the odor is not enough. We have frequently in various manipulations with the active substance met with what we took to be the odor of pyridine, but on shaking out with ether and adding an ethereal solution of hydrochloric acid and evaporating the ether we have been unable to detect pyridine in the residue.

Description of the Tracings.

Fig. 1. Tracing. Dog anæsthetized with morphine; curare and artificial respiration, both vagi cut. Injection of the active sulphate, freed from the carmine substance and coniine-like body, at ×.

A = running base line.
B = time record.
C = curve of the blood pressure, canula in the right carotid artery.

Fig. 2. Tracing. Conditions of the experiment as in Fig. 1. Injection at × of a highly active sulphate which still gives the rose-carmine color with iodine water and still contains some of the coniine-like substance which does not raise the blood pressure. The blood pressure is so high that the mercury is driven out of the manometer.

Fig. 3. Tracing. Conditions as in 1. Injection at × of a material which is still highly active although it had been boiled with 5 per cent. sodium hydrate for one hour. In this experiment a number of injections had already been made; the pressure had fallen to the normal before the injection indicated at × was made.

DESCRIPTION OF THE JOHNS HOPKINS HOSPITAL.

By John S. Billings, M. D., LL. D.

Containing 56 large quarto plates, phototypes, and lithographs, with views, plans and detail drawings of all the buildings, and their interior arrangements—also wood-cuts of apparatus and fixtures; also 116 pages of letter-press describing the plans followed in the construction, and giving full details of heating-apparatus, ventilation, sewerage and plumbing. Price, bound in cloth, $7.50.

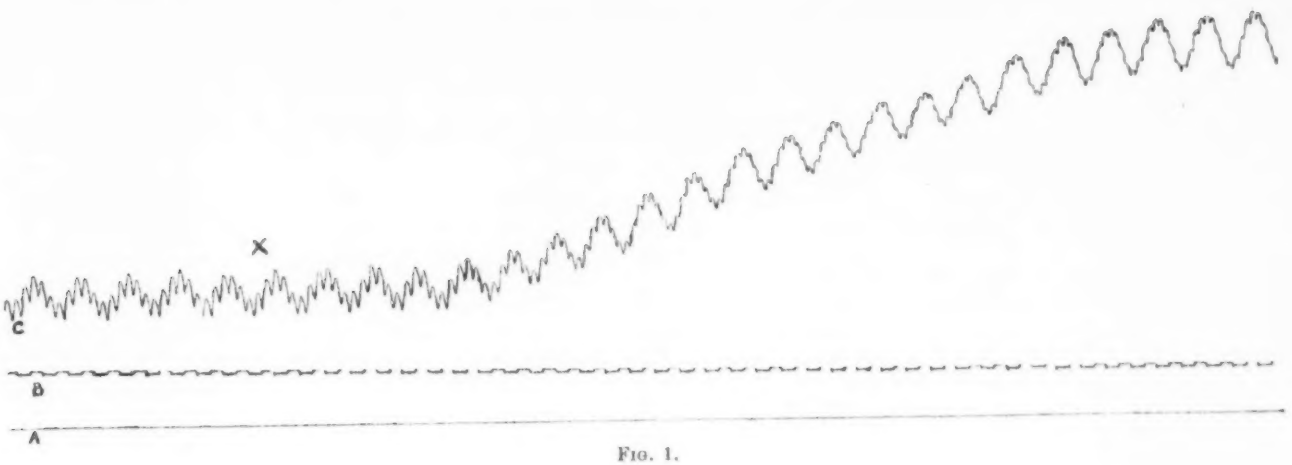

FIG. 1.

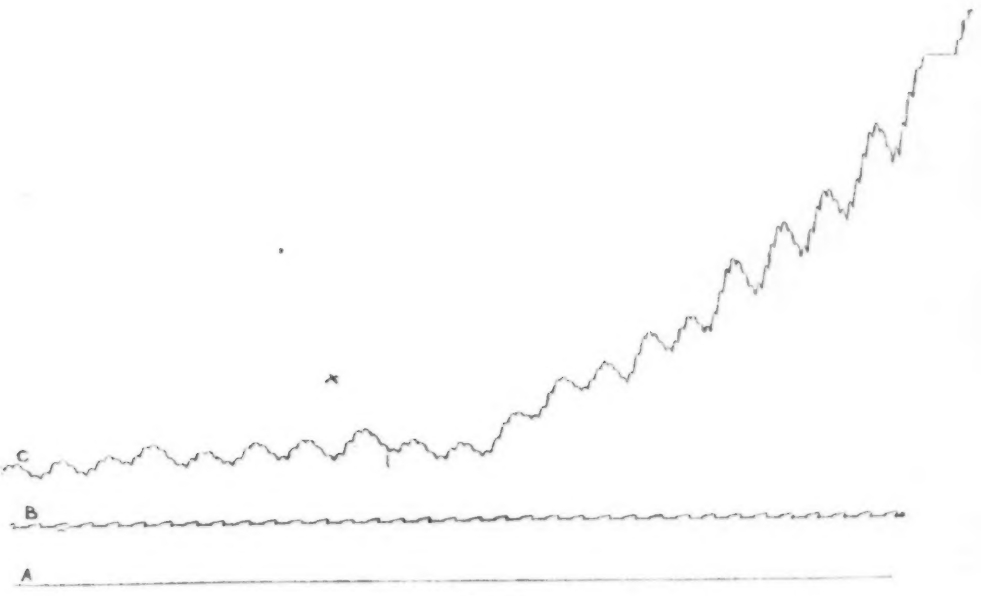

FIG. 2.

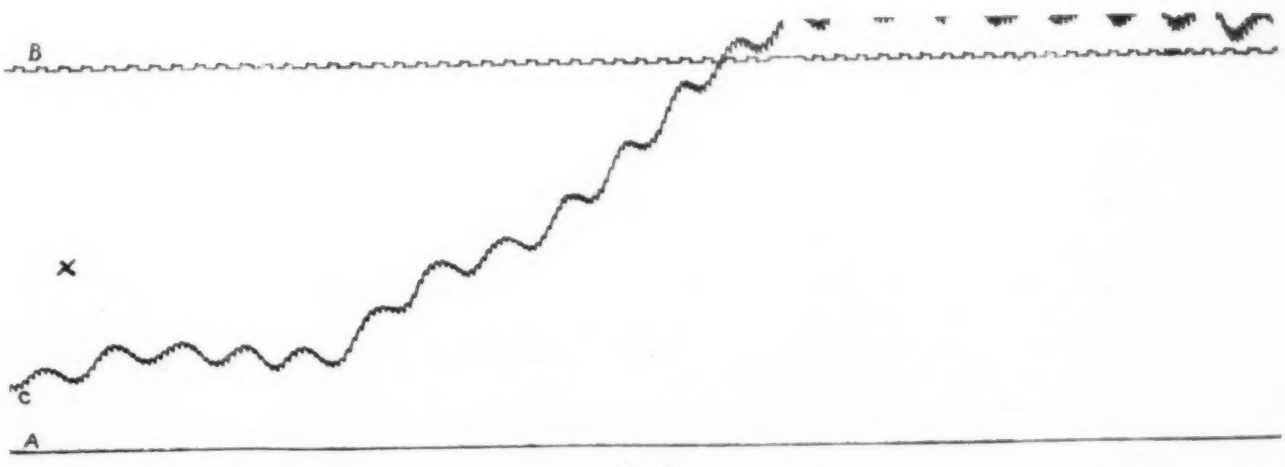

FIG. 3.

NOTES ON NEW BOOKS.

Anomalies and Curiosities of Medicine, being an encyclopedic collection of rare and extraordinary cases, and of the most striking instances of abnormality in all branches of Medicine and Surgery, derived from an exhaustive research of medical literature from its origin to the present day, abstracted, classified and indexed. By GEORGE M. GOULD, A. M., M. D., and WALTER L. PYLE, A. M., M. D. With 295 illustrations and 12 half-tone and colored plates. 968 pp. (*Philadelphia: W. B. Saunders*, 1897.)

The statement of Gibbon that objects which are only singular without being pleasing may excite surprise but soon lead to satiety and disgust, does not apply to this volume, which is thoroughly interesting from beginning to end. The attempt of the authors "to briefly epitomize and to arrange in order the records of the most curious, bizarre and abnormal cases that are found in medical literature of all ages and all languages," has been most successful. The book is thoroughly scientific in its treatment of the varied material which has been gathered with an industry which calls forth admiration. The first six chapters will probably be read most generally and relate to anomalies of conception, birth and development, and are of special interest to the gynecologist, obstetrician and student of legal medicine. Chapter seven relates to gigantism, dwarfishness, obesity and abnormal leanness, and the accompanying illustrations form a curious collection of anomalies suggestive of a dime museum.

The chapter on longevity taxes one's faith rather more than any other. Think of Henry Jenkins dying at the age of 169 years; Thomas Parr at 152; Jean Korin at 172 and his wife at 164, and a son left an orphan by their untimely death at the tender age of 116; Petretsh Zartan at 185 or 187 (authorities differing), who walked a mile to the post office a few days before his death to ask for alms; and many other well-authenticated instances of nearly equal age.

The chapter on anomalous mental and nervous diseases is so complete it is a matter of surprise that it does not include the history of the young man in Ohio who became totally blind at the age of seven months, and who, while receiving an education at the school for the blind, in consequence of a fall, lost both hearing and speech. After a time, his eyesight being restored by the fall, he was transferred to an establishment for the education of deaf mutes. Here eventually his hearing was suddenly restored, but epileptic attacks developed which required hospital treatment, this time in an institution for the insane. This well-authenticated tale was published in considerable detail in one of the State reports and deserves a place in these annals. The chapter on Historic Epidemics is timely, especially the full account of the bubonic plagues of the middle ages.

An excellent feature of the book is the judicial spirit shown by the authors. Facts are weighed and reasons are advanced for the conclusions which are reached. The book is well printed and finely illustrated and is worthy of a large success. Every chapter is of interest to every physician.

Text Book of Materia Medica, Therapeutics and Pharmacology. By G. F. BUTLER, M. D. (*Philadelphia: W. B. Saunders*, 1896.)

This work is dedicated to the "Medical Students of the United States," and we have no doubt that many of them who enjoy buying the latest work on this branch of medicine will find it serviceable. It cannot be said to replace the older works of Wood, Hare and others. There is very little true original thought in it, which should be the the real reason for the publication of any new book, especially to-day, when there is altogether too much production of simply transient works. As the author states in the preface: "From the U. S. Pharmacopeia chiefly, and from the National Dispensatory, have been adopted almost verbatim, the 'origin' and 'description and properties' of the various drugs under consideration," so it is more in his arrangement of his material that we must look for originality. He classifies the drugs by their properties, rather than alphabetically, as is done by Hare. Both methods have their advocates, and personally, as it is much the most rapid way to look up any given drug, we prefer the latter method. Butler still further classifies the drugs into so called "Disease-Medicines," a very unscientific term, as he himself recognizes, and "Symptom-Medicines." In such a classification no two persons will agree as to the class to which certain medicines will belong most properly, and thus it becomes confusing and time-consuming to search for the drug wanted. The author says: "A genuine specific is tolerated only by the system in which it antagonizes some disease. For instance, A and B are put under a prolonged course of mercury; A is salivated beyond recognition, while B's health improves—simply for the reason that B had syphilis, which A had not." Such general remarks are often not true, and the example given is a very poor one, for we all know that syphilitic patients may be salivated, and sometimes as severely as those who are not syphilitic. Also many patients who have not syphilis may take mercury in large doses for long periods of time without becoming salivated. We do not understand the following sentence: "Quinine was formerly considered a specific in malaria, until the fact was recognized that the drug is analogous to a normal constituent of healthy bile in its action upon plasmodia malariae." We believe that by most authorities quinine is still considered to be a specific in malaria, whatever the action of bile may be. In a work which covers so much ground as this text-book, the value depends on an equal balancing of the different parts, and especially, in the description of the drugs, of careful omission of all unnecessary parts, and still more exact and concise information on all important points. Each author naturally finds special interest in certain parts of his work, and so not knowing these it is hard to criticise the book justly. But in the 650 pages given to drugs and their actions we feel that much improvement could have been made with careful revision—some parts omitted, and other information of more importance added. We think it quite out of place to introduce in such a work declensions of simple Latin words and other rules of Latin grammar, which should be known by every student before he begins the study of medicine, and if he does not know them, he should not be helped to the knowledge in this superficial manner.

Diseases of the Ear, Nose and Throat. By S. S. BISHOP, M. D. (*Philadelphia: F. A. Davis Co.*, 1897.)

This book, we think, fulfills pretty satisfactorily the object of the author, as expressed in the preface; he says: "This work was designed, first to help students in preparing for their degree; second, for those progressive practitioners who wish to acquire the proficiency necessary to properly treat those patients who are unable to visit specialists; and third, for those who are gradually exchanging their general practice for special work in these branches." The chapter on blood-serum therapy in diphtheria seems out of place; it is merely an abstract of a few of the articles which have appeared on this subject during the past two years, and we see no good reason for introducing it here. The work on the whole is a fair presentation of our knowledge in these diseases, without any attempt to take up any of them at length. The treatment as given is generally satisfactory and simple. We do not agree with the author in considering hay-fever, or "nervous catarrh," as he prefers to call it, a result of uric acid diathesis. There are many questions in the study of this disease which are as yet quite inexplicable, and this theory of its causation is insufficient to explain them all; the neurotic character of the disease is well established, and that uric acid may in some cases play an important rôle in this nervous affection is undoubted, but it is also equally certain that other important causes play their rôle too in determining this malady.

This book is cheaply gotten up and the cuts are of poor quality; the colored illustrations also seem very unsatisfactory. Many of

the cuts are reproductions of instruments which by this time should be known to all practitioners and to every student graduating from a medical college. These simply add to the expense of the book without adding to its intrinsic value.

Essentials of Physical Diagnosis of the Thorax. Second Edition. By ARTHUR M. CORWIN, M. D. (*Philadelphia: W. B. Saunders*, 1896.)

That there is a demand for such a quiz-compend or aid in cramming for an examination is shown by the fact that a second edition of this small book has been called for. We cannot recommend it, however, for like other similar works it fails in attempting to condense much knowledge in a very limited space and although tolerably well arranged, there are numerous statements of fact with which we cannot agree. The varieties of tympany (p. 69) are confusing and not generally used and were better omitted in such a work. In the discussion of heart murmurs there is much needless repetition, and on p. 176 the mitral systolic murmur described as occurring in aortic insufficiency, otherwise known as Flint's murmur, is presystolic in time. The chapter on congenital lesions of the heart is treated too briefly to be of service, as is also the one on hydatid cyst of the lung, which, when primary, is not a condition easy to diagnose, nor could the signs of it as given by the author differentiate it from pleurisy. Spasm of the columnæ carneæ is a condition which may occur, but it is hardly one of which a diagnosis could be made. Acute endocarditis without valvular lesion is not a condition which can be recognized clinically, and inorganic aortic systolic murmurs should usually be doubted. The ratio of the inspiratory sound to the expiratory is not as three to one, nor in asthma is the dyspnœa (orthopnœa) chiefly expiratory. Cheyne-Stokes respiration does not ordinarily accompany opium poisoning. No worse instrument for clinical instruction could well be devised than the multiplex stethoscope, of which there is an illustration in the beginning of this work.

Pathological Report of the Illinois Eastern Hospital for the Insane. (*Chicago: Blakely Printing Co.*, 1896.)

This is an excellent report, full of much valuable material, and Dr. Adolf Meyer deserves much credit for it, considering the difficulties under which the work was prosecuted, due to a lack of general facilities for carrying it on. We cannot criticise any shortcomings when we read his closing remarks. He says: "It may justly be said that the publication of so much raw material is of little use. To polish the report, away from the records and the material, did not seem to be in the interest of the accuracy of a picture of the working of the laboratory which had barely come into existence at the end of the period covered. The work was planned on a broader basis than it was feasible to carry out in the short period. The idea was that the plan of publishing 'interesting' cases only was not in the interest of sober study of the daily experience, that selecting cases might lead to illustration of preconceived ideas instead of the facts as they present themselves in reality, and that at the present stage of psychiatry a consideration of all the things seen would be less dangerous than arbitrary selection. The same principle should be carried out in the clinical side as well." Although much of the material is raw, yet many facts of interest are to be found—perhaps the most interesting being that 32 per cent. out of 49 cases of terminal dementia, and 27 per cent. of 192 cases of mental diseases, including the first series, died of florid tuberculosis. Of course without fuller statistics as to the class of patients in the hospital, too much stress should not be laid on these figures, but nevertheless the percentage is high. A case of acute mania, dying presumably of sulphonal poisoning, shows the necessity of the utmost care being used in the administration of drugs to patients with mental diseases to avoid accidents of this sort. We shall await with pleasure successive reports from Dr. Meyer, who has now transferred his work to the Worcester State Hospital and Clark University, and trust he will be able to describe some of the finer microscopical findings in brain and cord lesions from the interesting material at his disposal.

St. Thomas's Hospital Reports. New Series. Vol. XXIV. (*London*, 1895.)

The first half only of this volume is taken up with detailed papers, and the second half with statistics of the different departments of the hospital, and brief abstracts of cases, medical and surgical. Among the papers here presented, two are worthy of special note. The article on "Osteo-arthropathy and its Relationships," with report of a case of pulmonary hypertrophic osteo-arthropathy, both by Dr. Walters, is a very valuable contribution to our knowledge of this curious condition and its relationship to akromegaly. It is an exhaustive study, with a brief abstract of all the cases reported of this bone disease up to the time of the publication of this volume. The other paper is on "Enteric Fever and Sewage Gas," in which 11 cases of typhoid fever are described as resulting from poisoning with sewer gas in one hospital within a short space of time. Here milk, water and food as possible sources of the contagion could apparently be eliminated without doubt, and the only other discoverable source was a water-closet into which typhoid organisms had probably been discharged but a few weeks before the outbreak of this small epidemic, which ceased as soon as the sewage pipes were overhauled and modified. With the modern belief that typhoid fever in nearly every case results from milk, water or food contaminated by the typhoid organism, this epidemic raises the most interesting question as to whether or not typhoid bacilli may enter the body through the lungs and thus cause the fever. There are other articles on tuberculous disease in the knee-joint, and relapse in the specific fevers, which will repay careful reading.

Feeding in Early Infancy. By ARTHUR V. MEIGS, M. D. (*Philadelphia: W. B. Saunders*, 1896.)

In this paper Dr. Meigs emphasizes the results of his milk analyses as expressed in his earlier publication, and describes in detail the preparation of his food, based on these results.

He finds that human milk never contains more than one per cent. casein, cow's milk three times this amount, other constituents being present in about equal quantities. In his preparation cow's milk is therefore diluted with lime water, and cream and sugar added in definite proportions. The food, prepared after this manner, has been used for a number of years by the author, with satisfactory results.

He thinks that subjecting milk to high temperatures detracts from its usefulness as an infant food; therefore it is better to be assured of its source and avoid sterilization.

This course seems hardly practicable, and the injurious effect accredited to sterilization is not sustained by most writers on the subject.

Proceedings of the American Medico-Psychological Association at the 52d Annual Meeting, held in Boston, May 26–29, 1896. (*American Medico-Psychological Association*, 1896.)

The proceedings of this society occupy nearly 300 large papers, pretty closely printed; but all the papers are good, while some are of especial value. There is an interesting address on psychological education by Stanley Hall, a leading authority on such a subject; and there are important contributions by Brush, Worcester, Hoch, and Berkley. The paper by Hoch, on "General Paralysis in Two Sisters," is perhaps, while one of the most thorough articles, the one of most general interest. To students who have given much time to the study of the blood, the paper on "Leucocytosis Associated with Convulsions," by Burrows, will open up a point of much interest as to the cause of leucocytosis, whether or not it be due to a form of auto-intoxication.

PUBLICATIONS OF THE JOHNS HOPKINS HOSPITAL.

THE JOHNS HOPKINS HOSPITAL REPORTS.

VOLUME I. 423 pages, 99 plates.

Report in Pathology.

The Vessels and Walls of the Dog's Stomach; A Study of the Intestinal Contraction; Healing of Intestinal Sutures; Reversal of the Intestine; The Contraction of the Vena Portae and its Influence upon the Circulation. By F. P. MALL, M. D.
A Contribution to the Pathology of the Gelatinous Type of Cerebellar Sclerosis (Atrophy). By HENRY J. BERKLEY, M. D.
Reticulated Tissue and its Relation to the Connective Tissue Fibrils. By F. P. MALL, M. D.

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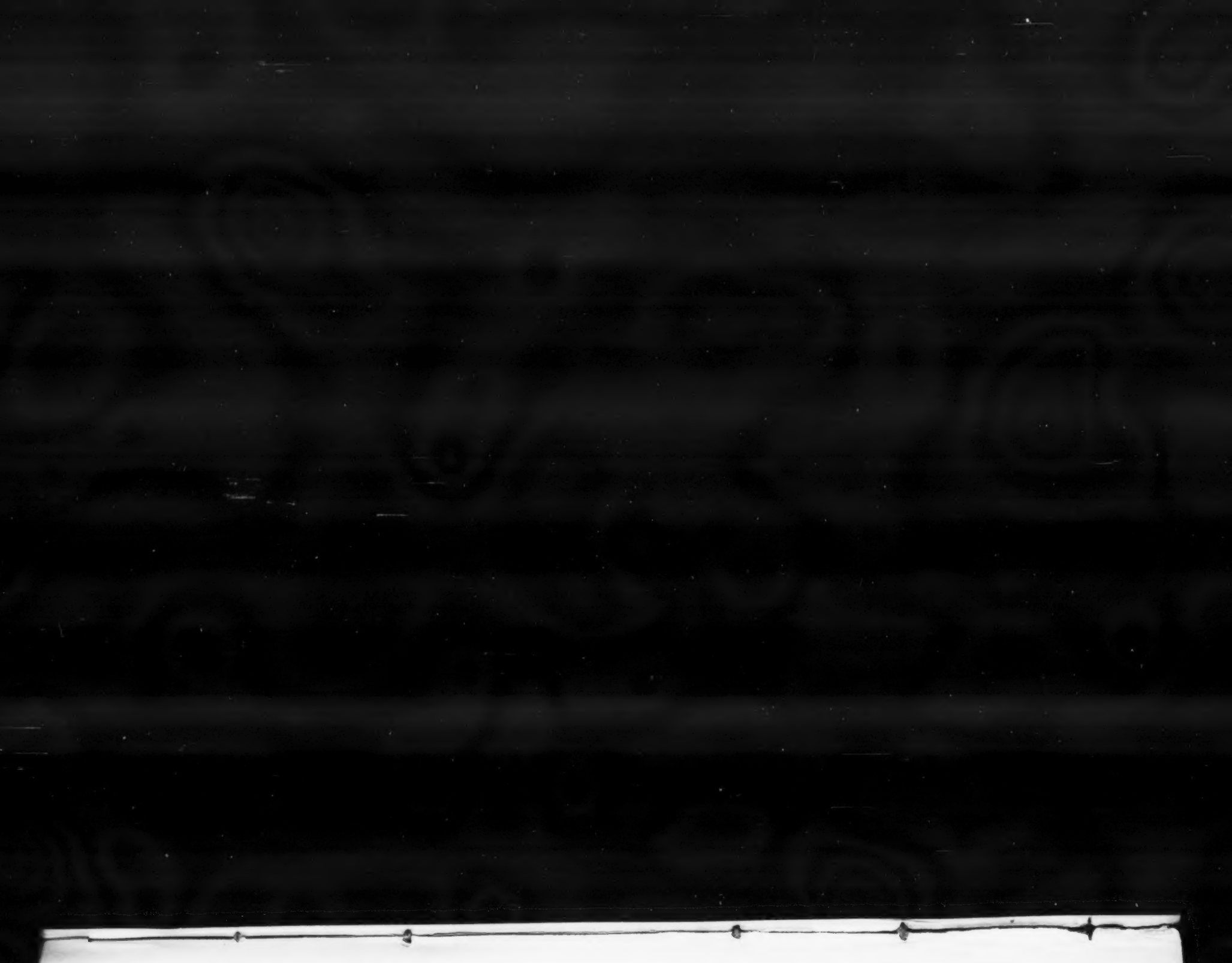
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